PB82-134347

Pesticide Registration Standard: Chloramben (3 amino 2,5-dichlorobenzoic acid)

(U.S.) Environmental Protection Agency
Washington, DC

Jul 81

U.S. Department of Commerce
National Technical Information Service
NTIS

United States
Environmental Protection
Agency

Office of
Pesticides and Toxic Substances
Washington DC 20460

July 1981

EPA

PB82-134347

Chloramben
(3 amino 2,5-dichlorobenzoic acid)

Pesticide Registration Standard

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U. S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

50272-101

REPORT DOCUMENTATION PAGE

1. REPORT NO. EPA - 540/RS - 81-015

2.

3. Recipient's Accession No. PB82 134347

4. Title and Subtitle
Pesticide Registration Standard
3 amino 2,5-dichlorobenzoic acid
(Chloramben)

5. Report Date July 1981

6. 336020

7. Author(s) USEPA, Special Pesticide Review Division (SPRD) and Registration Division (RD)

8. Performing Organization Rept. No.

9. Performing Organization Name and Address
US Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

10. Project/Task/Work Unit No.

11. Contract(C) or Grant(G) No.
(C)
(G)

12. Sponsoring Organization Name and Address
Same as #9

13. Type of Report & Period Covered

14.

15. Supplementary Notes

16. Abstract (Limit: 200 words)

This document contains information regarding reregistration of pesticide products containing 3 amino 2,5-dichlorobenzoic acid (Chloramben), including how to register under a registration standard, regulatory position and rationale, and summaries of data requirements and data gaps. Also included is a bibliography containing citations of all studies reviewed by EPA in arriving at the positions and conclusions contained in the standard.

17. Document Analysis a. Descriptors
Registration Standard
3 amino 2,5-dichlorobenzoic acid
(Chloramben)

b. Identifiers/Open-Ended Terms

c. COSATI Field/Group

18. Availability Statement

1<

19. Security Class (This Report) Unclassified

20. Security Class (This Page)

21. No. of Pages 186

22. Price

(See ANSI-Z39.18)

See Instructions on Reverse

OPTIONAL FORM 272 (4-77)
(Formerly NTIS-35)
Department of Commerce

Pesticide Registration Standard: Chloramben

(3 amino 2,5-dichlorobenzoic acid)

May, 1981

Office of Pesticides and Toxic Substances

Environmental Protection Agency

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CHAPTER I: HOW TO REGISTER UNDER A REGISTRATION STANDARD

1. Organization of the Standard
2. Purpose of the Standard
3. Requirement to Re-register Under the Standard
4. "Product Specific" Data and "Generic" Data
5. Data Compensation Requirements under FIFRA 3(c)(1)(D)
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7. Amendments to the Standard

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1. Organization of the Standard

This first chapter explains the purpose of a Registration Standard and summarizes the legal principles involved in registering or re-registering under a Standard. The second chapter sets forth the requirements that must be met to obtain or retain registration for products covered by this particular Registration Standard. In the remaining chapters, the Agency reviews the available data by scientific discipline, discusses the Agency's concerns with the identified potential hazards, and logically develops the conditions and requirements that would reduce those hazards to acceptable levels.

2. Purpose of the Standard

Section 3 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) provides that "no person in any State may distribute, sell, offer for sale, hold for sale, ship, deliver for shipment, or receive (and having so received) deliver or offer to deliver, to any person any pesticide which is not registered with the Administrator [of EPA]." To approve the registration of a pesticide, the Administrator must find, pursuant to Section 3(c)(5) that:

> "(A) its composition is such as to warrant the proposed claims for it; ,
>
> (B) its labeling and other material required to be submitted comply with the requirements of this Act;
>
> (C) it will perform its intended function without unreasonable adverse effects on the environment; and
>
> (D) when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment."

In making these findings, the Agency reviews a wide range of data which registrants are required to submit, and assesses the risks and benefits associated with the use of the proposed pesticide. But the established approach to making these findings has been found to be defective on two counts:

First, EPA and its predecessor agency, the United States Department of Agriculture (USDA), routinely reviewed registration applications on a "product by product" basis, evaluating each product-specific application somewhat independently. In the review of products containing similar components, there was little opportunity for a retrospective review of the full range of pertinent data available in Agency files and in the public literature. Thus the "product by product" approach was often inefficient and sometimes resulted in inconsistent or incomplete regulatory judgments.

Second, over the years, as a result of inevitable and continuing advances in scientific knowledge, methodology, and policy, the data base for many pesticides came to be considered inadequate by current scientific and regulatory standards. Given the long history of pesticide regulation in several agencies, it is even likely that materials may have been lost from the data files. When EPA issued new requirements for registration in 1975 (40 CFR 162) and proposed new guidelines for hazard testing in 1978 (43 FR 29686, July 10, 1978 and 43 FR 37336, August 2, 1978), many products that had already been registered for years were being sold and used without the same assurances of human and environmental safety as was being required for new products. Because of this inconsistency, Congress directed EPA to re-register all previously registered products, so as to bring their registrations and their data bases into compliance with current requirements, [See FIFRA Section 3(g)].

Facing the enormous job of re-reviewing and calling-in new data for the approximately 35,000 current registrations, and realizing the inefficiencies of the "product by product" approach, the Agency decided that a new, more effective method of review was needed.

A new review procedure has been developed. Under it, EPA publishes documents called Registration Standards, each of which discusses a particular pesticide active ingredient. Each Registration Standard summarizes all the data available to the Agency on a particular active ingredient and its current uses, and sets forth the Agency's comprehensive position on the conditions and requirements for registration of all existing and future products which contain that active ingredient. These conditions and requirements, all of which must be met to obtain or retain full registration or reregistration under Section 3(c)(5) of FIFRA, include the submission of needed scientific data which the Agency does not now have, compliance with standards of toxicity, composition, labeling, and packaging, and satisfaction of the data compensation provisions of FIFRA Section 3(c)(1)(D).

The Standard will also serve as a tool for product classification. As part of the registration of a pesticide product, EPA may classify each product for "general use" or "restricted use" [FIFRA Section 3(d)]. A pesticide is classified for "restricted use" when some special regulatory restriction is needed to ensure against unreasonable adverse effects to man or the environment. Many such risks of unreasonable adverse effects can be lessened if expressly-designed label precautions are strictly followed. Thus the special regulatory restriction for a "restricted use" pesticide is usually a requirement that it be applied only by, or under the supervision of, an applicator who has been certified by the State or Federal government as being competent to use pesticide safely, responsibly, and in accordance with label directions. A restricted-use pesticide can have other regulatory restrictions [40 CFR 162.11(c)(5)] instead of, or in addition to, the certified applicator requirement. These other regulatory restrictions may include such actions as seasonal or regional limitations on use, or a requirement for the monitoring of residue levels after use. A pesticide classified for "general use," or not classified at all, is available for use by any individual who is in compliance with State or local regulations. The Registration Standard review compares information about potential adverse effects of specific uses of the pesticide with risk criteria listed in 40 CFR 162.11(c), and thereby determines whether a product needs to be classified for "restricted use." If the Standard does classify a pesticide for "restricted use," this determination is stated in the second chapter.

3. Requirement to Reregister Under the Standard

FIFRA Section 3(g), as amended in 1978, directs EPA to reregister all currently registered products as expeditiously as possible. Congress also agreed that reregistration should be accomplished by the use of Registration Standards.

Each registrant of a currently registered product to which this Standard applies, and who wishes to continue to sell or distribute his product in commerce, must apply for reregistration. His application must contain proposed labeling that complies with this Standard.

EPA will issue a notice of intent to cancel the registration of any currently registered product to which this Standard applies if the registrant fails to comply with the procedures for reregistration set forth in the Guidance Package which accompanies this Standard.

4. "Product Specific" Data and "Generic" Data

In the course of developing this Standard, EPA has determined the types of data needed for evaluation of the properties and effects of products to which the Standard applies, in the disciplinary areas of Product Chemistry, Environmental Fate, Toxicology, Residue Chemistry, and Ecological Effects. These determinations are based primarily on the data Guidelines proposed in 43 FR 29696, July 10, 1978; 43 FR 37336, August 22, 1978; and 45 FR 72948, November 3, 1980, as applied to the use patterns of the products to which this Standard applies. Where it appeared that data from a normally applicable Guidelines requirement was actually unnecessary to evaluate these products, the Standard indicates that the requirement has been waived. On the other hand, in some cases studies not required by the Guidelines may be needed because of the particular composition or use pattern of products the Standard covers; if so, the Standard explains the Agency's reasoning. Data guidelines have not yet been proposed for the Residue Chemistry discipline, but the requirements for such data have been in effect for some time and are, the Agency believes, relatively familiar to registrants. Data which we have found are needed to evaluate the registrability of some products covered by the Standard may not be needed for the evaluation of other products, depending upon the composition, formulation type, and intended uses of the product in question. The Standard states which data requirements apply to which product categories. (See the third chapter.) The various kinds of data normally required for registration of a pesticide product can be divided into two basic groups:

A. Data that are product specific , i.e. data that relates only to the the properties or effects of a product with a particular composition (or a group of products with closely similar composition); and

B. Generic data that pertains to the properties or effects of a particular ingredient, and thus is relevant to an evaluation of the risks and benefits of all products containing that ingredient (or all such products having a certain use pattern), regardless of any such product's unique composition.

The Agency requires certain "product specific" data for each product to characterize the product's particular composition and physical/chemical properties (Product Chemistry), and to characterize the product's acute toxicity (which is a function of its total composition). The applicant for registration or reregistration of any product, whether it is a manufacturing-use or end-use product, and without regard to its intended use pattern, must submit or cite enough of this kind of data to allow EPA to evaluate the product. For such purposes, "product specific" data on any product other than the applicant's is irrelevant, unless the other product is closely similar in composition to the applicant's. (Where it has been found practicable to group similar products for purposes of evaluating, with a single set of tests, all products in the group, the Standard so indicates.) "Product specific" data on the efficacy of particular end-use products is also required where the exact formulation may affect efficacy and where failure of efficacy could cause public health problems.

All other data needed to evaluate pesticide products concerns the properties or effects of a particular ingredient of products (normally a pesticidally active ingredient, but in some cases a pesticidally inactive, or "inert", ingredient). Some data in this "generic" category are required to evaluate the properties and effects of all products containing that ingredient [e.g., the acute LD-50 of the active ingredient in its technical or purer grade; see proposed 40 CFR 163.81-1(a), 43 FR 37355].

Other "generic" data are required to evaluate all products which both contain a particular ingredient and are intended for certain uses (see, e.g., proposed 40 CFR 163.82-1, 43 FR 37363, which requires subchronic oral testing of the active ingredient with respect to certain use patterns only). Where a particular data requirement is use-pattern dependent, it will apply to each end-use product which is to be labeled for that use pattern (except where such end-use product is formulated from a registered manufacturing-use product permitting such formulations) and to each manufacturing-use product with labeling that allows it to be used to make end-use products with that use pattern. Thus, for example, a subchronic oral dosing study is needed to evaluate the safety of any manufacturing-use product that legally could be used to make an end-use, food-crop pesticide. But if an end-use product's label specified it was for use only in ways that involved no food/feed exposure and no repeated human exposure, the subchronic oral dosing study would not be required to evaluate the product's safety; and if a manufacturing-use product's label states that the product is for use only in making end-use products not involving food/feed use or repeated human exposure, that subchronic oral study would not be relevant to the evaluation of the manufacturing-use product either.

If a registrant of a currently registered manufacturing-use or end-use product wishes to avoid the costs of data compensation [under FIFRA Section 3(c)(1)(D)] or data generation [under Section 3(c)(2)(B)] for "generic" data that is required only with respect to some use patterns, he may elect to delete those use patterns from his labeling at the time he reregisters his product. An applicant for registration of a new product under this Standard may similarly request approval for only certain use patterns.

5. Data Compensation Requirements under FIFRA 3(c)(1)(D)

Under FIFRA Section 3(c)(1)(D), an applicant for registration, reregistration, or amended registration must offer to pay compensation for certain existing data the Agency has used in developing the Registration Standard. The data for which compensation must be offered is all data which are described by all the following criteria:

A. The data were first submitted to EPA (or to its predecessor agencies, USDA or FDA), on or after January 1, 1970;

B. The data were submitted to EPA (or USDA or FDA) by some other applicant or registant in support of an application for an experimental use permit, an amendment adding a new use to a registration, or for registration, or to support or maintain in effect an existing registration;

C. They are the kind of data which are relevant to the Agency's decision to register or reregister the applicant's product under the Registration Standard, taking into account the applicant's product's composition and intended use pattern(s);

D. The Agency has found the data to be valid and usable in reaching regulatory conclusions; and

E. They are not data for which the applicant has been exempted by FIFRA Section 3(c)(2)(D) from the duty to offer to pay compensation. (This exemption applies to the "generic" data concerning the safety of an active ingredient of the applicant's product, not to "product specific" data. The exemption is available only to applicants whose product is labeled for end-uses for which the active ingredient in question is present in the applicant's product because of his use of another registered product containing that active ingredient which he purchases from another producer.)

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An applicant for reregistration of an already registered product under this Standard, or for registration of a new product under this Standard, accordingly must determine which of the data used by EPA in developing the Standard must be the subject of an offer to pay compensation, and must submit with his application the appropriate statements evidencing his compliance with FIFRA Section 3(c)(1)(D).

An applicant would never be required to offer to pay for "product specific" data submitted by another firm. In many, if not in most cases, data which is specific to another firm's product will not suffice to allow EPA to evaluate the applicant's product, that is, will not be useful to the Agency in determining whether the applicant's product is registrable. There may be cases, however, where because of close similarities between the composition of two or more products, another firm's data may suffice to allow EPA to evaluate some or all of the "product specific" aspects of the applicant's product. In such a case, the applicant may choose to cite that data instead of submitting data from tests on his own product, and if he chooses that option, he would have to comply with the offer-to-pay requirements of Section 3(C)(1)(D) for that data.

Each applicant for registration or reregistration of a manufacturing-use product, and each applicant for registration or reregistration of an end-use product, who is not exempted by FIFRA Section 3(c)(2)(D), must comply with the Section 3(c)(1)(D) requirements with respect to each item of "generic" data that relates to his product's intended uses.

A detailed description of the procedures an applicant must follow in applying for reregistration (or new registration) under this Standard is found in the Guidance Package for this Standard.

6. Obtaining Data to Fill "Data Gaps"; FIFRA 3(c)(2)(B)

Some of the kinds of data EPA needs for its evaluation of the properties and effects of products to which this Standard applies have never been submitted to the Agency (or, if submitted, have been found to have deficiencies rendering them inadequate for making registrability decisions) and have not been located in the published literature search that EPA conducted as part of preparing this Standard. Such instances of missing but required data are referred to in the Standard as "data gaps".

FIFRA Section 3(c)(2)(B), added to FIFRA by the Congress in 1978, authorizes EPA to require registrants to whom a data requirement applies to generate (or otherwise produce) data to fill such "gaps" and submit those data to EPA. EPA must allow a reasonably sufficient period for this to be accomplished. If a registrant fails to take appropriate and timely steps to fill the data gaps identified by a section 3(c)(2)(B) order, his product's registration may be suspended until the data is submitted. A mechanism is provided whereby two or more registrants may agree to share in the costs of producing data for which they are both responsible.

The Standard lists, in the third chapter, the "generic" data gaps and notes the classes of products to which these data gaps pertain. The Standard also points out that to be registrable under the Standard, a product must be supported by certain required "product specific" data. In some cases, the Agency may possess sufficient "product specific" data on one currently registered product, but may lack such data on another. Only those Standards which apply to a very small number of currently registered products will attempt to state definitively the "product specific" data gaps on a "product by product" basis. (Although the Standard will in some cases note which data that EPA does possess would suffice to satisfy certain "product specific" data requirements for a category of products with closely similar composition characteristics.)

As part of the process of reregistering currently registered products, EPA will issue Section 3(c)(2)(B) directives requiring the registrants to take appropriate steps to fill all identified data gaps — whether the data in question are "product specific" or "generic" — in accordance with a schedule.

Persons who wish to obtain registrations for new products under this Standard will be required to submit (or cite) sufficient "product specific" data before their applications are approved. Upon registration, they will be required under Section 3(c)(2)(B) to take appropriate steps to submit data needed to fill "generic" data gaps. (We expect they will respond to this requirement by entering into cost-sharing agreements with other registrants who previously have been told they must furnish the data.) The Guidance Package for this Standard details the steps that must be taken by registrants to comply with Section 3(c)(2)(B).

7. Amendments to the Standard

Applications for registration which propose uses or formulations that are not presently covered by the Standard, or which present product compositions, product chemistry data, hazard data, toxicity levels, or labeling that do not meet the requirements of the Standard, will automatically be considered by the Agency to be requests for amendments to the Standard. In response to such applications, the Agency may request additional data to support the proposed amendment to the Standard, or may deny the application for registration on the grounds that the proposed product would cause unreasonable adverse effects to the environment. In the former case, when additional data have been satisfactorily supplied, and providing that the data do not indicate the potential for unreasonable adverse effects, the Agency will then amend the Standard to cover the new registration.

Each Registration Standard is based upon all data and information available to the Agency's reviewers on a particular date prior to the publication date. This "cut-off" date is stated at the beginning of the second chapter. Any subsequent data submissions and any approved amendments will be incorporated into the Registration Standard by means of addenda, which are available for inspection at EPA in Washington, D.C., or copies of which may be requested from the Agency. When all the present "data gaps" have been filled and the submitted data have been reviewed, the Agency will revise the Registration Standard. Thereafter, when the Agency determines that the internally maintained addenda have significantly altered the conditions for registration under the Standard, the document will be updated and re-issued.

While the Registration Standard discusses only the uses and hazards of products containing the designated active ingredient(s), the Agency is also concerned with the potential hazards of some inert ingredients and impurities. Independent of the development of any one Standard, the Agency has initiated the evaluation of some inert pesticide ingredients. Where the Agency has identified inert ingredients of concern in a specific product to which the Standard applies, these ingredients will be pointed out in the Guidance Package.

CHAPTER II

AGENCY POSITION ON CHLORAMBEN

Introduction

This chapter describes in detail the Agency's regulatory position on pesticide products which contain chloramben as the sole active ingredient. The regulatory position adopted by the Agency incorporates a number of considerations. Foremost among these considerations is an analysis of the registrability of chloramben based on the risk criteria found in Section 162.11(a) of Title 40 of the U.S. Code of Federal Regulations. Following the Agency's statement on the registrability of chloramben is the rationale for this basic determination.

In addition to this decision, standards of product composition, acute toxicity, labeling, and use are established. Applicants for the registration of chloramben products must meet these standards to obtain registration. The rationale for establishing a particular standard follows the presentation of the standard. Regulatory actions such as requiring protective clothing during application are prescribed, and additional data are requested. The basis for any regulatory action can be found by reading the rationale for the action, which follows the chosen regulatory option.

In general, the scientific basis for any regulatory action, including establishing data requirements, can be found in the disciplinary chapters. References to Agency guidelines for testing are provided when appropriate.

Description of Chemical

Chloramben is a herbicide used for the control of a variety of annual grasses and broadleaf weeds in agricultural and ornamental crops, both in non-domestic and domestic settings. Chloramben is the common name for 3-amino 2,5-dichlorobenzoic acid. Currently registered manufacturing-use products are limited to Sodium Chloramben (the sodium salt of chloramben) and Methyl Chloramben (the methyl ester of chloramben).

Chloramben formulated products are marketed under the trade names Amiben, Vegiben, Weedone, and Ornamental Weeder. These products represent a wide range of product types (soluble concentrates, flowable concentrates, emulsifiable concentrates, and granulars) and contain a variety of forms of chloramben (sodium chloramben, methyl chloramben, ammonium chloramben and monomethyl ammonium chloramben).

Products containing mixtures of chloramben and other active ingredients are not covered under this Standard.

Regulatory Position for Chloramben

Chloramben, as described in this Standard may be registered for sale, distribution, reformulation and use in the United States. Considering all information available to the Agency as of October 1, 1980, the Agency finds that none of the risk criteria found in Section 162.11(a) of Title 40 of the U.S. Code of Federal Regulations were met or exceeded for chloramben.

The Agency has determined that chloramben does not cause an unreasonable adverse effect with proper label directions and precautions. Chloramben products currently registered may be reregistered subject to the conditions imposed. New products may be registered under this Standard and are subject to the same requirements.

Regulatory Rationale for Chloramben

Chloramben was referred for review to the Rebuttable Presumption Against Registration (RPAR) Program in October of 1980. The referral of this pesticide to the RPAR Program was based on an oncogenicity study on technical chloramben (3-amino 2,5-dichlorobenzoic acid), conducted by Gulf South Research Institute (GSRI) for the National Cancer Institute (NCI). This study indicates that chloramben administration results in hepatocellular carcinoma in female mice. The NCI study reports statistically significant incidences of hepatocellular carcinoma in female mice receiving 10,000 and 20,000 ppm dietary doses of chloramben.

This study was reviewed by the Environmental Protection Agency (EPA) and was found to contain minor flaws in protocol and study conduct. The Agency's review indicates that although the study is flawed, the NCI results do indicate a clear positive result at the 20,000 ppm dose in female mice, and that the study is adequate for risk assessment purposes.

Additional data were collected and reviewed by the Agency to complete the assessment of the oncogenicity of chloramben. No other studies indicating chloramben related chronic effects were identified, and an oncogenicity study, completed in 1978 by Huntington Research Center, reported no statistically significant increases in tumour incidence in mice receiving dietary doses of 100, 1,000, and 10,000 ppm of chloramben. In addition, a chronic feeding study in rats completed in 1979 by Litton Bionetics reported no chloramben dose-related chronic effects in rats at dietary doses of 100, 1,000, and 10,000 ppm. Available mutagencity testing (Ames test) utilizing technical chloramben yielded negative results.

A major concern regarding any potential long-term exposure in humans to a pesticide product is the risk of developing delayed toxic effects, principally cancer. The results presented in the NCI bioassay of chloramben are utilized in the completion of an oncogenic risk assessment. The results of this risk assessment are factored into the decision to proceed or not to proceed with a presumption against the registration of chloramben.

In order to assess this risk for exposure to chloramben, a worst-case situation based on the conclusions of the NCI bioassay of chloramben is utilized. Using the NCI data as the basis for a risk assessment, we obtain a potency of 1.05×10^{-5}.

Reported Incidence of Hepatocellular Carcinoma in Female Mice

Dose (ppm)		
0	10,000	20,000
2/67 (0.03)	7/48 (0.15)	10/50 (0.20)

The dose-response relationship assumed in the risk analysis is that of the linear multi-stage model. The lifetime probability of cancer due to ingesting chloramben has been determined to be on the order of $1x\ 10^{-9}$ (see chapter 7 for detailed determination).

For applicator exposure, a dietary exposure equivalent is calculated for risk assessment. Applicator exposure data were not available on chloramben per se. However, exposure studies involving pesticides used in a similar manner to chloramben were available for extrapolation and use in an applicator risk assessment.

The Agency assumed that the largest segment of the applicator population at greatest risk through exposure to chloramben was applicators of soluble/flowable concentrate products in soybeans. Use of chloramben in soybeans represents 96% of chloramben usage. Both granular and soluble/flowable concentrate products are currently registered for use in soybeans. Of these two formulation types, the liquid formulations present the highest potential for significant exposure. The lifetime probability of cancer due to chloramben application in soybeans of soluble/flowable concentrate products has been determined to be on the order of $1x\ 10^{-7}$ (see chapters 5 and 7 for detailed determination). This represents a worst-case assessment.

The Agency is 95% confident that these risk levels (dietary: $1x\ 10^{-9}$; and applicator: $1x\ 10^{-7}$) will not be exceeded by the dose (virtually safe dose) as determined in chapters 5 and 7.

Section 3(c)(8) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) directs the Agency not to initiate a Rebuttable Presumption Against Registration (RPAR) action unless the action is based on a validated test or other sigificant evidence raising prudent concerns of unreasonable adverse effects to man or the environment. Human exposure to pesticides through any medium or pathway is a central issue in evaluating unreasonable adverse effects of pesticide products. It is the Agency's policy to attempt to reduce exposure, whenever possible, to acceptable levels without issuing an RPAR action.

The Agency determined that the existing data base on chloramben does not support a Rebuttable Presumption Against Registration. Results from the risk assessment completed by the Agency, combined with the weight of the data base, indicate that issuing a Rebuttable Presumption Against the Registration of chloramben at this time would not be prudent regulatory policy.

The Agency thus decided to reregister all pesticide products containing chloramben as the sole active ingredient, provided the conditions are met as described under the heading: "Criteria for Registration Under the Chloramben Standard". These conditions include the submission of applicator exposure data on a typical liquid formulation as a data requirement.

Criteria for Registration Under the Chloramben Standard

To be subject to this Standard, chloramben products must:

1. contain chloramben as the sole active ingredient;
2. be within acceptable standards of composition as specified;
3. be within acute toxicity limits as specified;
4. be labelled for acceptable end-uses as specified; and
5. bear required labeling as specified.

Manufacturing-use chloramben products must bear label directions for formulation into acceptable end-uses.

Applicants for registration or reregistration of chloramben products under this Standard must comply with all terms and conditions described in the following sections, including commitment to fill data gaps on a time schedule specified by the Agency and when applicable offer to pay compensation to the extent required by 3(c)(1)(D) and 3(c)(2)(D) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, 7 U.S.C. 136(c)(1)(D) and 136(c)(2)(D). As discussed in Chapter I, applicants for the registration of chloramben products under this Standard must contact the Agency for specific instructions, including updated information on data requirements and companies whose data must be cited and to whom compensation must be offered.

A. Manufacturing-use Chloramben

1. Acceptable Range and Limits

Summary Table

Product Composition	Acute Toxicity	End-Use Patterns
Active Ingredient: Any Percentage with appropriate certification of limits.	Acute Oral: Category I-IV	Outdoor terrestrial uses (food or nonfood)
	Acute Dermal: Category I-IV	
	Acute Inhalation: Category I-IV	
	Primary Eye: Category I-IV	
	Primary Dermal: Category I-IV	

a. Product Composition Standards

Currently registered chloramben manufacturing-use products include the sodium salt of chloramben and the methyl ester of chloramben. Manufacturing-use chloramben products with any percentage of sodium or methyl chloramben are acceptable under this Standard with appropriate certification of limits.

The Agency has determined that information on the physical/chemical properties of technical chloramben (3 amino 2,5-dichlorobenzoic acid) cannot be used to fulfill product chemistry requirements for manufacturing-use sodium chloramben or methyl chloramben. Available data indicate that the physical/chemical properties of sodium and methyl chloramben are different from the physical/chemical properties of technical grade chloramben. Information on the physical/chemical properties of both sodium and methyl chloramben are required in addition to information on technical grade chloramben (3 amino 2,5-dichlorobenzoic acid).

b. Acute Toxicity Limits

Manufacturing-use chloramben products with established acute toxicity category I-IV ratings for each of the acute effects (acute oral, dermal, and inhalation toxicity and primary eye and dermal irritation) are acceptable under this Standard.

c. Use Patterns

Manufacturing-use chloramben products must be labeled for formulation into end-use herbicides intended for outdoor terrestrial uses (food or nonfood).

Chloramben is currently registered for use in a variety of food crops, and for use in annual and perennial flowers, shrubs, and trees.

Tolerances have been established for chloramben use on the following crops: soybeans, tomatoes, lima beans, corn, peanuts, beans (dry, edible), cantaloupe, cucumbers, peppers, pumpkin, beans (snap), squash, sunflower, and sweet potatoes.

The Agency will consider additional tolerances on food or feed crops provided that applicants for the registration of the additional crop(s) submit a petition(s), supply appropriate residue data, and demonstrate that the addition of the tolerance(s) will not result in an unacceptable risk to the general population. Applicants must also demonstrate that the additional food-use pattern(s) will not result in an unacceptable risk to applicators.

The Agency will accept applications for additional tolerances because available data indicate that the currently estimated dietary intake of chloramben per day is .09% of the ADI (see Tolerance Reassessment).

The Agency will consider additional non-food, terrestrial outdoor uses of chloramben provided that applicants for the registration of the additional use(s) submit any additional data required for the registration of the use, and demonstrate that the use pattern will not result in an unacceptable risk to applicators.

2. Required Labeling

All manufacturing-use chloramben products must bear appropriate labeling as specified in 40 CFR 162.10.

Registrants have the option of supplying requested rotational crop studies or of placing the following prohibition on labels of all end-use products containing chloramben:

"Do not rotate to other crops"

3. Tolerance Reassessment

Tolerances of 0.1 ppm have been established for residues of chloramben in all food crops for which chloramben is registered. This level was originally established at the limit of detectability of chloramben. The theoretical maximum residue contribution (TMRC) of chloramben to the human diet is .013 mg/day. This figure is adjusted for the percentage of chloramben treated crops to arrive at the maximum estimated chloramben intake figure of .00022 mg/kg/day (see Chapter 6 for full dietary exposure analysis).

The "No Observable Effect Level" (NOEL) in dogs was reported to be 25 mg/kg body weight (Hazleton Laboratories, 0028). The acceptable daily intake (ADI) calculated from this figure is .25 mg/kg/day. The maximum estimated chloramben intake per day is .09% of the calculated ADI.

B. Soluble Concentrate Chloramben

1. Acceptable Ranges and Limits

Summary Table

Product Composition	Acute Toxicity	End-Use Patterns
Active Ingredient: Any percentage with appropriate certification of limits.	Acute Oral: Category III-IV	Outdoor terrestrial food-uses or nonfood
Inert Ingredients: Inert ingredients in food-use formulations must be cleared for such use under 40 CFR 180.1001.	Acute Dermal: Category III-IV Acute Inhalation: Category III-IV	
Currently registered soluble concentrate products containing 23.4% Ammonium Chloramben are substantially similar.	Primary Eye: Category III-IV Primary Dermal: Category III-IV	

a. Product Composition Standards

Currently registered chloramben soluble concentrate products include several products containing 23.4% ammonium chloramben and one product containing 15.7% ammonium chloramben and 47.2% monomethyl-ammonium chloramben. The Agency has determined that existing soluble concentrate products containing the ammonium salt of chloramben are substantially similar. The sole soluble concentrate product containing a mixture of the ammonium and monomethyl ammonium salts has been determined to be unique.

Soluble concentrate chloramben products with any percentage of sodium chloramben, ammonium chloramben, monomethyl-ammonium chloramben, or methyl chloramben are acceptable for consideration under this Standard, with appropriate certification of limits.

Inert ingredients in food-use formulations must be cleared for such use under 40 CFR 180.1001.

b. Acute Toxicity Limits

Soluble concentrate products with established acute toxicity category III-IV ratings for each of the acute effects (acute oral, dermal and inhalation toxicity and primary eye and dermal irritation) are acceptable for consideration under this Standard.

c. Use Patterns

Soluble concentrate chloramben products containing ammonium and/or monomethylammonium chloramben can be registered for non domestic or domestic-use in soybeans, dry beans, peanuts, sunflowers, corn, lima beans, squash, pumpkins, asparagus (seedling), and sweet potatoes.

Currently registered dosage rates and application methods are acceptable (see page 5-4) pending submission of required residue chemistry data listed in the manufacturing-use section of chapter III.

Proposed soluble concentrate chloramben products containing sodium chloramben or methyl chloramben can also be registered for non domestic-use or domestic-use in soybeans, dry beans, peanuts, sunflowers, corn, lima beans, squash, pumpkins, asparagus (seedling), and sweet potatoes provided any additional requested residue data reflecting the proposed use of the pesticide on the crop is submitted and found to be acceptable.

Soluble concentrate chloramben products can be registered for use in any crop for which a tolerance for chloramben (or exemption from a tolerance), has been granted.

2. Required Labeling

All soluble concentrate chloramben products must bear appropriate labeling as specified in 40 CFR 162.10.

3. Regulatory Rationale

Product Composition Standards: The Agency finds no reason to limit soluble concentrate formulations to the ammonium or monomethyl ammonium salts of chloramben as the active ingredients, provided any additional required data reflecting the proposed use of the product on the crop is provided.

The Agency finds no reason to limit the % active ingredient in formulations as long as the amount of active ingredient applied per acre does not exceed acceptable levels and result in residues which exceed the tolerance.

Acute Toxicity Standards: The Agency limited acute toxicity to categories III through IV because domestic use is acceptable under this Standard.

Use Patterns: The Agency finds no reason to limit the use of soluble concentrate products to currently registered crops. The use of soluble concentrate chloramben products on other crops (for which a tolerance or exemption from a tolerance has been granted) is acceptable provided any additional residue data are submitted on the use of the product on the crop.

C. Flowable Concentrate Chloramben

1. Acceptable Ranges and Limits

Summary Table

Product Composition	Acute Toxicity	End-Use Patterns
Active Ingredient: Any percentage with appropriate certification of limits.	Acute Oral: Category III-IV	Outdoor terrestrial food-uses or nonfood
Inert Ingredients: Inert Ingredients in food-use formulations must be cleared for such use under 40 CFR 180.1001.	Acute Dermal: Category III-IV Acute Inhalation: Category III-IV	
Currently registered flowable concentrate products containing sodium chloramben are substantially similar.	Primary Eye: Category III-IV Primary Dermal: Category III-IV	

a. Product Composition Standards

Currently registered chloramben flowable concentrate products contain 21% and 83% sodium chloramben. The Agency has determined that existing flowable concentrate chloramben products are substantially similar.

Flowable concentrate chloramben products with any percentage of sodium chloramben, ammonium chloramben, monomethyl-ammonium chloramben, or methyl chloramben are acceptable for consideration under this Standard, with appropriate certification of limits.

Inert ingredients in food-use formulations must be cleared for such use under 40 CFR 180.1001.

b. Acute Toxicity Standards

Flowable concentrate products with established acute toxicity category III-IV ratings for each of the acute effects (acute oral, dermal, inhalation toxicity, and primary eye and dermal irritation) are acceptable for consideration under this Standard.

c. Use Patterns

Flowable concentrate chloramben products containing sodium chloramben can be registered for domestic or non domestic use in soybeans, dry beans, peanuts, and sunflowers.

Currently registered dosage rates and application methods are acceptable (see page 5-4) pending submission of required residue chemistry data listed in the manufacturing-use section of chapter III.

Proposed flowable concentrate chloramben products containing ammonium chloramben, monomethyl ammonium chloramben, or methyl chloramben can also be registered for non domestic or domestic use in soybeans, dry beans, peanuts, and sunflowers provided any additional requested residue data reflecting the use of the pesticide on the crop is submitted and found to be acceptable.

Flowable concentrate chloramben products can be registered for use in any crop for which a tolerance for chloramben (or exemption from a tolerance) has been granted.

2. Required Labeling

All flowable concentrate chloramben products must bear appropriate labeling as specified in 40 CFR 162.10.

3. Regulatory Rationale

Product Composition Standards: The Agency finds no reason to limit flowable concentrate formulations to the sodium salt of chloramben as the active ingredient provided any additional required residue data reflecting the proposed use of the product on the crop(s) is provided.

The Agency finds no reason to limit the % active ingredient in formulations as long as the amount of active ingredient applied per acre does not exceed acceptable levels and result in residues which exceed tolerances.

Acute Toxicity Standards: The Agency limited acute toxicity to categories III through IV because domestic use is acceptable under this Standard.

Use Patterns: The Agency finds no reason to limit the use of flowable concentrate products to currently registered crops. The use of flowable concentrate products on other crops (for which a tolerance or exemption from tolerance has been granted) is acceptable provided any additionally required residue data are submitted on the use of the product on the crop.

D. Emulsifiable Concentrates

1. Acceptable Ranges and Limits

Summary Table

Product Composition	Acute Toxicity	End-Use Patterns
Active Ingredient: Any percentage with appropriate certification of limits	Acute Oral: Category III-IV	Outdoor terrestrial food uses or nonfood
Inert Ingredients: Inert Ingredients in food-use formulations must be cleared for such use under 40 CFR 180.1001.	Acute Dermal: Category III-IV Acute Inhalation: Category III-IV	
The currently registered emulsifiable concentrate product contains 23.2% methyl chloramben.	Primary Eye: Category III-IV Primary Dermal: Category III-IV	

a. Product Composition Standards

The currently registered emulsifiable concentrate chloramben product contains 23.2% methyl chloramben.

Emulsifiable concentrate chloramben products with any percentage of sodium, methyl, ammonium, or monomethyl ammonium chloramben are acceptable for consideration under this Standard, with appropriate certification of limits.

Inert Ingredients in food-use formulations must be cleared for such use under 40 CFR 180.1001.

b. Acute Toxicity Limits

Emulsifiable concentrate products with established acute toxicity category III-IV ratings for each of the acute effects (acute oral, dermal and inhalation toxicity and primary eye and dermal irritation) are acceptable for consideration under this Standard.

c. Use Patterns

Emulsifiable concentrate products containing methyl chloramben can be registered for non domestic-use in snap beans, cantaloupes, and cucumbers.

Currently registered dosage rates and application methods are acceptable (see page 5-4) pending submission of required residue chemistry data listed in the manufacturing-use section of chapter III.

Proposed emulsifiable concentrate chloramben products containing sodium, ammonium or monomethyl ammonium chloramben can be registered for domestic or non-domestic use in snap beans, cantaloupes, and cucumbers provided any additional requested residue data reflecting the proposed use of the pesticide on the crop is provided.

Emulsifiable concentrate products can be registered for use in any crop for which a tolerance (or exemption from a tolerance) has been granted.

2. Required Labeling

All emulsifiable concentrate chloramben products must bear appropriate labeling as specified in 40 CFR 162.10.

3. Regulatory Rationale

Product Composition Standards: The Agency finds no reason to limit emulsifiable concentrate formulations to the methyl ester of chloramben as the active ingredient, provided any additional residue data reflecting the proposed use of the product on the crop is provided, and found to be acceptable.

The Agency finds no reason to limit the % active ingredient in formulations as long as the amount of active ingredient applied per acre does not exceed acceptable levels and result in residues above tolerance levels.

Acute Toxicity Standards: The Agency limited acute toxicity to categories III-IV because emulsifiable concentrate products containing sodium, ammonium, and monomethyl ammonium chloramben can be registered for domestic use.

Use Patterns: The Agency finds no reason to limit the use of emulsifiable concentrate chloramben products to currently registered crops. The use of flowable concentrate products on other crops (for which a tolerance or exemption from a tolerance has been granted) is acceptable provided any additionally required residue data are submitted on the use of the product on the crop.

E. Granular Chloramben

1. Acceptable Ranges and Limits

Summary Table

Product Composition	Acute Toxicity	End-Use Patterns
Active Ingredient: Any percentage with appropriate certification of limits.	Acute Oral: Category III-IV	Outdoor terrestrial food (or non food) uses
Inert Ingredients: Inert ingredients in food-use formulations must be cleared for such use under 40 CFR 180.1001.	Acute Dermal: Category III-IV	
	Acute Inhalation: Category III-IV	
Currently registered granular products containing ammonium chloramben are substantially similar.	Primary Eye: Category III-IV	
Currently registered granular products containing ammonium and monomethyl ammonium chloramben are substantially similar.	Primary Dermal: Category III-IV	

a. Product Composition Standards

Currently registered granular chloramben products contain 1.3%-10.8% ammonium chloramben, and mixtures of 2.82%-5.4% ammonium chloramben and 8.46%-17.3% monomethyl ammonium chloramben.

Granular chloramben products with any percentage of sodium, methyl, ammonium or monomethyl ammonium chloramben are acceptable for consideration under this standard with appropriate certification of limits.

Inert Ingredients in food-use formulations must be cleared for such use under 40 CFR 180.1001.

b. Acute Toxicity Limits

Granular chloramben products with established acute toxicity category III-IV ratings for each of the acute effects (acute oral, dermal, and inhalation toxicity and primary eye and dermal irritation) are acceptable for consideration under this Standard.

c. Use Patterns

Granular chloramben products containing ammonium and monomethyl ammonium chloramben can be registered for domestic or non-domestic use in soybeans, dry beans, peanuts, sunflowers, corn, sweet potatoes, transplanted tomatoes and peppers, lima beans, pumpkins, squash, asparagus (seedling), and ornamentals.

Currently registered dosage rates and application methods are acceptable (see page 5-4) pending submission of required residue chemistry data listed in chapter III.

Proposed granular chloramben products containing sodium or methyl chloramben can be registered for domestic or non-domestic use in soybeans, dry beans, peanuts, sunflowers, corn, sweet potatoes, transplanted tomatoes and peppers, lima beans, pumpkins, squash, asparagus (seedling), and ornamentals, provided any additional requested residue data reflecting the proposed use of the product on the crop is provided and found to be acceptable.

Granular chloramben products can be registered for use in any crop for which a tolerance (or exemption from a tolerance) has been granted.

2. Required Labeling

All granular chloramben products must bear appropriate labeling as specified in 40 CFR 162.10.

3. Regulatory Rationale

Product Composition Standards: The Agency finds no reason to limit granular chloramben products to the ammonium or monomethyl ammonium salts of chloramben as the active ingredients, provided any additional residue data reflecting the proposed use of the product on the crop is provided, and found to be acceptable.

The Agency finds no reason to limit the % active ingredient in formulations as long as the amount of active ingredient per acre does not exceed acceptable levels and result in residues above tolerance levels.

Acute Toxicity Standards: The Agency limited the acute toxicity of granular products to categories III-IV because granular products containing ammonium chloramben, monomethyl ammonium chloramben, sodium chloramben and methyl chloramben can be registered for domestic use.

Use Patterns: The Agency finds no reason to limit the use of granular chloramben to currently registered crops. The use of granular chloramben on other crops covered by this Standard (for which a tolerance or exemption from a tolerance has been granted) is acceptable provided any additional residue data are submitted and found to be acceptable.

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CHAPTER III

DATA REQUIREMENTS AND DATA GAPS

A. Manufacturing-use Chloramben

1. Generic Data Requirements:

Table 3-1, entitled: Generic Data Requirements and Data Gaps for Manufacturing-use Products includes those data that pertain to the properties or effects of chloramben as an active ingredient. Thus, these data are relevant to an evaluation of the risks and benefits of all products containing chloramben. Providing data to fill indicated gaps in the data base is the primary responsibility of the registrant(s) of manufacturing-use chloramben. Registrants of end-use products which are not exempted by FIFRA Section 3(c)(2)(D) are also responsible for the submission of these data. Applicants for the registration or reregistration of manufacturing-use chloramben products must acknowledge reliance on existing data which fill indicated data requirements under FIFRA Section 3(c)(1)(D). These data are listed under the column entitled: Bibliographic Citation in this table.

Environmental Fate Data

Data on physico-chemical degradation, mobility, metabolism, and accumulationare required on both sodium chloramben and methyl chloramben. Requested data on the fate of sodium chloramben will support the registrations of all products containing sodium, ammonium, and monomethyl ammonium chloramben. Requested data on methyl chloramben will support the registrations of all products containing methyl chloramben.

In addition, the Agency is requiring the completion of an applicator exposure study. The study should be conducted with a typical soluble or flowable concentrate formulation, mixed and then applied by ground equipment to a typical (160 acres) soybean field at recommended application rates. This study is required because the decision not to presume against the registration of chloramben was based, in part, on the results of the applicator oncogenic risk assessment. The risk assessment used data extrapolated from exposure studies on pesticides used in a similar manner to chloramben. The Agency is requiring this study to verify the exposure estimates used in the oncogenic risk assessment.

Product Chemistry Data

Certain data on the physical/chemical properties of technical chloramben (3-amino 2,5-dichloro benzoic acid) are required for the registration of both sodium and methyl chloramben.

Toxicology Data

The sodium salt of chloramben has been determined to be equivalent to chloramben for the purposes of extrapolating "generic" toxicity data.

A summary report in Agency files indicates that the methyl ester of chloramben hydrolyzes to chloramben within days of application to the soil. Provided that evidence is submitted documenting the breakdown of methyl chloramben to chloramben after application, and provided an acceptable metabolism study is submitted on methyl chloramben, all subchronic and chronic toxicology generic data requirements may be fulfilled for the methyl ester and sodium salt by testing with chloramben (or the sodium salt).

Ecological Effects Data

Fish and wildlife (ecological effects) safety testing must be conducted on sodium chloramben (for the registration of products containing sodium chloramben) and on the methyl ester (for the registration of products containing methyl chloramben). Separate testing is required because data indicate that the physical/chemical properties (ie. solubility) of methyl chloramben and sodium chloramben differ. These differences could influence the acute toxicity of these compounds to fish and wildlife.

Residue Chemistry Data

Data on the storage of RAC between harvest and sampling are required for the registration of both sodium and methyl chloramben.

2. Product Specific Data Requirements: Manufacturing-use Chloramben

Table 3-2, entitled: Product Specific Data Requirements for Manufacturing-use Products includes those data that relate only to the properties or effects of a product with a specific composition (or substantially similar composition). Thus, these data are required of each product (or substantially similar product) to characterize the product's particular composition and physical/chemical properties, and to characterize the product's acute toxicity.

Product composition data are required for each manufacturing-use product. Providing data to fulfill these requirements is the responsibility of each applicant for the registration or reregistration of a manufacturing-use chloramben product. If the Agency has data which fulfills this requirement for a particular product(s) then this is indicated in the chart and in the guidance package accompanying this Standard.

Data on the physical/chemical properties and acute toxicity of manufacturing-use products are required for each product or substantially similar product. Providing data to fulfill these requirements is the responsibility of each applicant for the registration or reregistration of a manufacturing-use chloramben product.

Product specific data need not be acknowledged under FIFRA Section 3(c)(1)(D) unless the Agency or a registrant has established that one product is substantially similar to another product for which the Agency has received acceptable data.

Existing manufacturing-use chloramben products, methyl and sodium chloramben, are not substantially similar for the purposes of establishing product-specific testing requirements.

Product Chemistry Data

Data requirements 163.61-3 through 163.61-7 (product composition data) apply to each proposed or currently registered manufacturing-use chloramben product.

Data requirements 163.61-8(7) through 163.61-8(18) (physical/chemical properties data) apply to manufacturing-use products which are not the same as the technical grade of the active ingredient. These data are required on both sodium and methyl chloramben.

Toxicology Data

Data requirements 163.81-1 and 163.81-2 (acute oral and dermal toxicity) apply to manufacturing-use products which are not toxicologically equivalent to the technical grade of the active ingredient. Sodium chloramben has been determined to be equivalent to chloramben. Separate testing on methyl chloramben must be supplied.

Data requirements 163.81-3 through 163.81-6 apply to each manufacturing-use product or substantially similar product. Testing must be supplied on both sodium and methyl chloramben. Methyl chloramben is not equivalent to sodium chloramben for the purposes of extrapolating acute toxicity data.

B. End-Use Chloramben Products

Applicants for the registration of end-use products containing chloramben are advised that if the Agency does not receive commitments, within the specified time frame, from manufacturing-use chloramben registrants to fill data gaps identified for the manufacturing-use product (Table 3-1), manufacturing-use product registrations will be suspended. Formulators must then bear the burden of supplying these data if continued availability of the manufacturing-use product is desired.

1. Generic Data Requirements

Table 3-3, entitled: Generic Data Requirements and Data Gaps for End-use Products Containing Ammonium Chloramben includes generic data which are required for the registration of all end-use products containing ammonium or monomethyl ammonium chloramben. Ammonium and monomethyl ammonium chloramben end-use products are prepared by an integrated formulation system. Certain product chemistry data are required on technical grade ammonium and technical grade monomethyl ammonium chloramben for the registration of end-use products containing these salts.

The Agency has determined that acute oral and dermal toxicity testing on technical grade chloramben or sodium chloramben will not fulfill the requirements for acute testing on technical grade ammonium and monomethyl ammonium chloramben. However, chronic or long term toxicology testing on the ammonium or monomethyl ammonium salts is not required.

The Agency has determined that fate data on technical ammonium and monomethyl ammonium chloramben are not required. Requested data on sodium chloramben will suffice.

Because data on the toxicity of sodium or methyl chloramben to fish and wildlife cannot be used to assess the toxicity of end-use products containing ammonium or monomethyl ammonium chloramben, additional data on these salts are required. Because there are no manufacturing-use products which contain ammonium or monomethyl ammonium chloramben, these data must be supplied by the producers of end-use ammonium or monomethyl ammonium chloramben products.

2. Product Specific Data Requirements for End-Use Products

Table 3-4: Product Specific Data Requirements and Data Gaps for Soluble Concentrate Chloramben

Table 3-5: Product Specific Data Requirements and Data Gaps for Flowable Concentrate Chloramben

Table 3-6: Product Specific Data Requirements and Data Gaps for Emulsifiable Concentrate Chloramben

Table 3-7: Product Specific Data Requirements and Data Gaps for Granular Chloramben

Tables 3-4 through 3-7 include those data that relate only to the properties or effects of products with a specific composition (or substantially similar composition). Thus, these data are required of each product (or substantially similar product) to characterize the product's particular composition and physical/chemical properties, and to characterize the products acute toxicity.

Product composition data are required for each end-use product. Providing data to fulfill this requirement is the responsibility of each applicant for the registration or reregistration of an end-use chloramben product. If the Agency has data which fulfills this requirement for a particular product(s) then this is indicated in the chart and in the guidance package accompanying this Standard.

Data on the physical/chemical properties and acute toxicity of end-use products are required for each product or substantially similar product. Providing data to fulfill these requirements is the responsibility of each applicant for the registration or reregistration of an end-use chloramben product.

Product specific data need not be acknowledged under FIFRA Section 3(c)(1)(D) unless the Agency or a registrant has established that one product is substantially similar to another product for which the Agency has received acceptable data.

Substantially Similar Products

Existing Soluble Concentrate Chloramben products (containing 23.4% ammonium chloramben) are substantially similar to each other.

Existing Soluble Concentrate Chloramben products (containing a mixture of ammonium and monomethyl ammonium salts) are substantially similar to each other.

Existing Flowable Concentrate Chloramben products (containing sodium chloramben) are substantially similar to each other.

Existing Granular Chloramben products (containing ammonium chloramben) are substantially similar to each other and to S.C. products containing ammonium chloramben.

Existing Granular Chloramben products (containing a mixture of ammonium and monomethyl ammonium chloramben) are substantially similar to each other and to S.C. products containing ammonium and monomethyl ammonium chloramben.

Product Chemistry Data

Data requirements 163.61-6 through 163.61-7 (product composition data) apply to each proposed or currently registered end-use chloramben product.

Toxicology Data

Data requirements 163.81-1 through 163.81-6 apply to each end-use chloramben product or substantially similar product.

TABLE-3-1

GENERIC DATA REQUIREMENTS AND DATA GAPS FOR MANUFACTURING-USE CHLORAMBEN

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
ENVIRONMENTAL FATE						
163.62-7(b)	Hydrolysis	Yes	Sodium & Methyl Chloramben*	Partial: Sodium No: Methyl	Union Carbide, 1981, 0172	Yes: May, 1983
163.62-7(c)	Photodegradation	Yes	Sodium & Methyl Chloramben	No		Yes: May, 1983
163.62-8(b)	Aerobic Soil Metabolism	Yes	Sodium & Methyl Chloramben	No		Yes: May, 1983
163.62-8(c)	Anaerobic Soil Metabolism	Yes	Sodium & Methyl Chloramben	No		Yes: May, 1983
163.62-8(d)	Anaerobic Aquatic Metabolism	No				
163.62-8(e)	Aerobic Aquatic Metabolism	No				
163.62-9(b)	Leaching	Yes	Sodium & Methyl Chloramben	No		Yes: May, 1983
163.62-9(c)	Volatility	No				
163.62-9(d)	Adsorp./Desorp.	Yes	Sodium & Methyl Chloramben	No		Yes: May, 1983
163.62-9(e)	Water Dispersal	No				
163.62-10(b)	Terrestrial Field Dissipation	Yes	Representative Formulations	No		Yes: May, 1983
163.62-10(c)	Aquatic Field Dissipation	No				
163.62-10(d)	Terrestrial/ Aquatic Dissip.	No				
163.62-10(e)	Aquatic Impact	No				
163.62-10(f)	Comb.& Tank Mixes	No				
163.62-10(g)	Long Term Study	No				
163.62-11(b)	Rotational Crop	Yes	Representative Formulations	No		Yes: May, 1983
163.62-11(c)	Irrigated Crops	No				
163.62-11(d)	Fish Accumulation	Yes	Sodium & Methyl Chloramben	Yes: Sodium No: Methyl	Iwan, 1978, 0020	Yes: May, 1983
	Applicator Exposure Study	Yes	Typical Liquid Formulation	No		Yes: May, 1982

* Technical grade chloramben acid or sodium chloramben and methyl chloramben.

These data requirements are current as of May, 1981. Refer to guidance package for updated requirements.

TABLE 3-1 (con)

GENERIC DATA REQUIREMENTS AND DATA GAPS
FOR MANUFACTURING-USE CHLORAMBEN

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
PRODUCT CHEMISTRY						
163.61-3(b)	Identification	Yes	Tech. Grade*	Yes		No
163.61-3(c)	Composition	Yes	Tech. Grade	No		Yes: October, 1981
163.61-7	Analytical Methods & Data	Yes	Tech. Grade	Partial: Need data	Amchem, 1972, 0083	Yes: October, 1981
163.61-8(1)	Color	Yes	Tech. Grade	Yes	Amchem Products, 1967, 0081 Amchem Products, 1959, 0124 Amchem Products, 1960, 0125	
163.61-8(2)	Odor	Yes	Tech. Grade	No		Yes: October, 1981
163.61-8(3)	Melting Point	Yes	Tech. Grade	Yes	Amchem Products, 1967, 0081 Amchem Products, 1959, 0124 Amchem Products, 1960, 0125	
163.61-8(4)	Solubility	Yes	Tech. Grade	Yes	Amchem Products, 1967, 0081 Amchem Products, 1959, 0124 Amchem Products, 1960, 0125	
163.61-8(5)	Stability	Yes	Tech. Grade	No		Yes: October, 1981
163.61-8(6)	Octanol/Water Partition Coefficient	Yes	Tech. Grade	No		Yes: October, 1981
163.61-8(7)	Physical State	Yes	Tech. Grade	Yes	Amchem Products, 1967, 0081 Amchem Products, 1959, 0124 Amchem Products, 1960, 0125	
163.61-8(8)	Density or Specific Gravity	Yes	Tech. Grade	No		Yes: October, 1981
163.61-8(9)	Boiling Point	No				
163.61-8(10)	Vapor Pressure	Yes	Tech. Grade	Partial	Amchem, 1967, 0081	Yes: October, 1981
163.61-8(11)	pH	Yes	Tech. Grade	No		Yes: October, 1981

* Technical Grade Chloramben Acid

These data requirements are current as of May, 1981. Refer to guidance package for updated requirements.

TABLE-3-1 (con)

GENERIC DATA REQUIREMENTS AND DATA GAPS
FOR MANUFACTURING-USE CHLORAMBEN

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
TOXICOLOGY						
163.81-1	Acute Oral Toxicity	Yes	Tech. Grade*	Yes	Hazleton, 1959, 0022	No
163.81-2	Acute Dermal Toxicity	Yes	Tech. Grade	Yes	Hazleton, 1959, 0023	No
163.81-7	Acute Delayed Neurotoxicity	No				
163.82-1	Subchronic Oral Toxicity	Yes	Tech. Grade	Partial: Need product purity	Litton, 1979, 0171	Yes: October, 1981
163.82-2	Subchronic (21-day) Dermal Toxicity	Yes	Tech. Grade	No		Yes: May, 1983
163.82-3	Subchronic 90-day Dermal Tox.	No				
163.82-4	Subchronic Inhal. Tox.	No				
163.82-5	Subchronic Neurotoxicity	No				
163.83-1	Chronic Feeding	Yes	Tech. Grade	Partial: Need product purity for 0171	Litton, 1979, 0171	Yes: October, 1981
163.83-2	Oncogenicity	Yes	Tech. Grade	Partial: Need product purity for 0170,0171	HRC, 1978, 0170 Litton, 1979, 0171 NCI, 1977, 0019	Yes: October, 1981
163.83-3	Teratogenicity	Yes	Tech. Grade	No		Yes: May, 1983
163.83-4	Reproduction	Yes	Tech. Grade	Partial: Need product purity for 0029	AMR, 1956, 0029	Yes: October, 1981
163.84-1-4	Mutagenicity	Yes	Tech. Grade	Partial	Anderson, 1972, 0502	Yes: May, 1983
163.85-1	Metabolism	Yes	Tech. Grade & Methyl Ester**	No		Yes: May, 1983
163.86-1	Domestic Animal Safety Testing	No				

* Technical Chloramben Acid or Sodium Chloramben
** Technical Chloramben Acid or Sodium Chloramben and Methyl Chloramben

These data requirements are current as of May, 1981. Refer to guidance package for updated requirements.

TABLE-3-1(con)

GENERIC DATA REQUIREMENTS AND DATA GAPS
FOR MANUFACTURING-USE CHLORAMBEN

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
ECOLOGICAL EFFECTS						
163.71-1	Avian Single Dose Oral LD50	Yes	Sodium & Methyl Chloramben[1]	No		Yes: October, 1981
163.71-2	Avian Dietary LC50	Yes	Sodium &	Yes: Sodium	Wild. Intn'l, 1978, 0059 Aff. Med. Res., 1973, 0036	Yes: October, 1981
			Methyl Chloramben	Partial: Methyl, need wild water waterfowl study	Aff. Med. Res., 1973, 0039	
163.71-3	Mammalian Acute Toxicity	No				
163.71-5	Simul. & Actual Field Testing for Mammals/Birds	No				
163.72-1	Fish Acute LC50	Yes	Sodium &	Yes: Sodium	U. Carbide, 1978, 0060 U. Carbide, 1978, 0061	Yes: October, 1981
			Methyl Chloramben	No: Methyl		
163.72-2	Acute Toxicity to Aquatic Invertebrates	Yes	Sodium & Methyl Chloramben	No		Yes: October, 1981
163.72-3	Acute Toxicity to Estuarine & Marine Organisms	No				
163.72-4	Embryolarvae & Life-Cycle	No				
163.72-5	Aquatic Organ. Tox. & Residue Studies	No				
163.72-6	Simul. & Actual Field Testing for Aquatic Organisms	No				

[1] Testing required on both sodium and methyl chloramben.

These data requirements are current as of May, 1981. Refer to guidance package for updated requirements.

TABLE-3-1 (con)

GENERIC DATA REQUIREMENTS AND DATA GAPS
FOR MANUFACTURING-USE CHLORAMBEN

Name of Test Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
RESIDUE CHEMISTRY					
Metabolism in Plants	Yes	Rep. Form.*	Yes	Swanson, 1966, 0169 Amchem, 1960, 0127 Amchem, 1963, 0008 Amchem, 1965, 0076 Amchem, 1961, 0079 Amchem, 1963, 0098 Amchem, 1963, 0106 Amchem, 1961, 0159 Amchem, 1964, 0161 Amchem, 1963, 0162 Amchem, 1963, 0163 Amchem, 1964, 0164 Amchem, 1961, 0154 Amchem, 1961, 0104 Amchem, 1961, 0157 Amchem, 1978, 0101	No
Metabolism in Animals	No				
Analytical Methods	Yes	Rep. Form.*	Yes	Amchem, 1963, 0158 Amchem, 1965, 0077 Amchem, 1964, 0107 Amchem, 1978, 0057 Amchem, 1968, 0085 Amchem, 1967, 0166 Amchem, 1967, 0167	No

TABLE 3-1 (con)

GENERIC DATA REQUIREMENTS AND DATA GAPS FOR MANUFACTURING-USE CHLORAMBEN

Name of Test Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
RESIDUE CHEMISTRY (con)					
Residue Data: RAC					
Soybeans	Yes	Rep. Form.*	Yes	Amchem, 1965, 0071 Amchem, 1968, 0084 Stauffer, 1979, 0041 Amchem, 1967, 0044 Elanco, 1978, 0050 Amchem, 1978, 0057 Amchem, 1978, 0101 Amchem, 1961, 0104 Amchem, 1975, 0109 Amchem, 1967, 0120 Amchem, 1976, 0118 Amchem, 1961, 0135 Amchem, 1961, 0136	No
Peanuts	Yes	Rep. Form.	Yes	Amchem, 1967, 0044 Amchem, 1965, 0076 Amchem, 1965, 0077 Amchem, 1968, 0084 Amchem, 1975, 0109	No
Peppers	Yes	Rep. Form.	Yes	Amchem, 1967, 0044 Amchem, 1964, 0093 Amchem, 1975, 0109 Amchem, 1963, 0162 Amchem, 1964, 0008	No
Tomatoes	Yes	Rep. Form.	Yes	Amchem, 1967, 0044 Amchem, 1963, 0106 Amchem, 1975, 0109 Amchem, 1963, 0102	No

TABLE-3-1 (con)

GENERIC DATA REQUIREMENTS AND DATA GAPS
FOR MANUFACTURING-USE CHLORAMBEN

Name of Test Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
RESIDUE CHEMISTRY (con)					
Residue Data: RAC					
Lima Beans	Yes	Rep. Form.	Yes	Amchem, 1967, 0044 Amchem, 1963, 0038 Amchem, 1963, 0108 Amchem, 1975, 0109	No
Corn	Yes	Rep. Form.	Yes	Amchem, 1967, 0044 Amchem, 1964, 0080 Amchem, 1975, 0109 Amchem, 1969, 0110	No
Sweet Potatoes	Yes	Rep. Form.	Yes	Amchem, 1967, 0044 Amchem, 1964, 0078 Amchem, 1975, 0109	No
Pumpkin, Squash	Yes	Rep. Form.	Yes	Amchem, 1967, 0044 Amchem, 1968, 0084 Amchem, 1964, 0164	No

TABLE-3-1 (con)

GENERIC DATA REQUIREMENTS AND DATA GAPS
FOR MANUFACTURING-USE CHLORAMBEN

Name of Test Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
RESIDUE CHEMISTRY (con)					
Residue Data: RAC					
Dry Beans	Yes	Rep. Form.	Yes	Amchem, 1967, 0044 Amchem, 1968, 0084 Amchem, 1964, 0008 Amchem, 1964, 0096 Amchem, 1968, 0149	No
Snap Beans	Yes	Rep. Form.	Yes	Amchem, 1968, 0149	No
Cucumbers	Yes	Rep. Form.	Yes	Amchem, 1968, 0149	No
Melons	Yes	Rep. Form.	Yes	Amchem, 1968, 0149	No
Sunflower	Yes	Rep. Form.	Yes	Amchem, 1979, 0100	No
Storage Data	Yes	Rep. Form.	No		Yes: May, 1983
Residue Data:					
Processed Foods	No				
Residues in Meat, Milk, Poultry, and Eggs	No				

Data requirements are current as of May, 1981. Refer to guidance package for updated requirements.

* From application of representative formulations.

TABLE-1-2

PRODUCT-SPECIFIC DATA REQUIREMENTS AND DATA GAPS FOR MANUFACTURING-USE CHLORAMBEN PRODUCTS

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?*	Bibliographic Citation	Must Additional Data Be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
PRODUCT CHEMISTRY						
163.61-3	Prod. Identity and Disclosure of Ingredients	Yes	Each MUP**	Yes: Methyl Chloramben Yes: Sodium *		No
163.61-4	Description of Manufacturing Process	Yes	Each MUP	No		Yes: October, 1981
163.61-5	Disc. of Format of Unint. Ingredients	Yes	Each MUP	No		Yes: October, 1981
163.61-6	Declaration of Ingredient Limits	Yes	Each MUP	No: Methyl Chloramben Yes: Sodium *		Yes: October, 1981
163.61-7	Product Analyt. Methods and Data	Yes	Each MUP	Partial: Methyl Partial: Sodium	Anchem, 1979, 0054 Anchem, 1977, 0083	Yes: October, 1981
163.61-8(7)	Physical State	Yes	MUP***	Yes	Anchem Products, 1966, 0037 Anchem Products, 1974, 0054 Anchem Products, 1962, 0081 Anchem Products, 1959, 0124 Anchem Products, 1960, 0125	No
163.61-8(8)	Density or Specific Gravity	Yes	MUP	No: Methyl Chloramben Yes: Sodium *	Anchem Products, 1979, 0054	Yes: October, 1981
163.61-8(9)	Boiling Point	No				
163.61-8(10)	Vapor Pressure	Yes	MUP	No		Yes: October, 1981
163.61-8(11)	pH	Yes	MUP	No		Yes: October, 1981
163.61-8(12)	Storage Stab.	Yes	MUP	No: Methyl Yes. Sodium	Anchem Products, 1978, 0069	Yes: October, 1981
163.61-8(13)	Flammability	Yes	MUP	No		Yes: October, 1981
163.61-8(14)	Oxidizing or Reducing Action	Yes	MUP	No		Yes: October, 1981
163.61-8(15)	Explosiveness	Yes	MUP	No		Yes: October, 1981
163.61-8(16)	Miscibility	Yes	MUP			Yes: October, 1981
163.61-8(17)	Viscosity	Yes	MUP	No		Yes: October, 1981
163.61-8(18)	Corrosion Characteristics	Yes	MUP	No		Yes: October, 1981

* For Currently Registered Products

** Required for each Manufacturing-use Product.

*** Required for Manufacturing-use Products which are not the same as the Technical Grade of the Active Ingredient. This data is required for both Manufacturing-use Sodium and Methyl Chloramben.

These data requirements are current as of May, 1981. Refer to guidance package for updated requirements.

TABLE-3-2 (con)

PRODUCT-SPECIFIC DATA REQUIREMENTS AND DATA GAPS
FOR MANUFACTURING-USE CHLORAMBEN PRODUCTS

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?*	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
TOXICOLOGY						
163.81-1	Acute Oral Toxicity	Yes	MUP**	Partial: Methyl Submit product purity for 0024 Yes: Sodium Chloramben	Hazleton, 1959, 0022 Hazleton, 1966, 0024	Yes: October, 1981
163.81-2	Acute Dermal Toxicity	Yes	MUP**	No: Methyl Chloramben Yes: Sodium "	Hazleton, 1959, 0023 CDC Res., 1978, 0065	Yes: October, 1981
163.81-3	Acute Inhal. Toxicity	Yes	MUP***	No: Methyl Chloramben Yes: Sodium "	Food & Drug, 1978, 0062	Yes: October, 1981
163.81-4	Prim. Eye Irritation****	Yes	MUP***	No: Methyl Chloramben Yes: Sodium "	CDC Res., 1978, 0064	Yes: October, 1981
163.81-5	Primary Dermal Irritation	Yes	MUP***	No: Methyl Chloramben Yes: Sodium "	CDC Res., 1978, 0063	Yes: October, 1981
163.81-6	Dermal Sensitization	Yes	MUP***	No		Yes: October, 1981

* For Currently Registered Products.

** Required for Manufacturing-use Products which are not the same as the Technical Grade of the Active Ingredient. Sodium Chloramben has been determined to be the same as Technical Chloramben Acid. Methyl Chloramben has been determined to be different.

*** Each Manufacturing-use Product or Substantially Similar Product.

**** A demonstration of pH between 1 and 3, or 12 and 14 or a demonstration of dermal irritability will be sufficient to categorize a product as an ocular irritant, and additional testing will not be required.

These data requirements are current as of May, 1981. Refer to guidance package for updated requirements.

TABLE-3-3

GENERIC DATA REQUIREMENTS AND DATA GAPS
FOR END-USE CHLORAMBEN PRODUCTS CONTAINING AMMONIUM CHLORAMBEN

Guideline Citation	Name of Test Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
ECOLOGICAL EFFECTS						
163.71-1	Avian Single Dose Oral LD50	Yes	Ammonium and Monomethyl ammonium*	No		Yes: October, 1981
163.71-2	Avian Dietary LC50	Yes	"	No		Yes: October, 1981
163.71-3	Mammalian Acute Toxicity	No				
163.71-5	Simul. & Actual Field Testing for Mammals/Birds	No				
163.72-1	Fish Acute LC50	Yes	Ammonium and Monomethyl ammonium*	No		Yes: October, 1981
163.72-2	Acute Toxicity to Aquatic Invertebrates	Yes	"	No		Yes: October, 1981
163.72-3	Acute Toxicity to Estuarine & Marine Organisms	No				
163.72-4	Embryolarvae & Life-Cycle	No				
163.72-5	Aquatic Organ. Tox. & Residue Studies	No				
163.72-6	Simul. & Actual Field Testing for Aquatic Organisms	No				

* Testing Required on Technical Grade Ammonium and Technical Grade Monomethyl Ammonium Chloramben. Data on Technical Chloramben Acid, Sodium Chloramben or Methyl Chloramben cannot be extrapolated to Ammonium Chloramben or Monomethyl Ammonium Chloramben.

These data requirements are current as of May 1981. Refer to guidance package for updated requirements.

TABLE-3-3 (con)

GENERIC DATA REQUIREMENTS AND DATA GAPS
FOR END-USE CHLORAMBEN PRODUCTS CONTAINING AMMONIUM CHLORAMBEN

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
PRODUCT CHEMISTRY						
163.61-3(b)	Identification	Yes	Tech. Grade*	No		Yes: October, 1981
163.61-3(c)	Composition	Yes	Tech. Grade	No		Yes: October, 1981
163.61-7	Analytical Methods & Data	Yes	Tech. Grade	No		Yes: October, 1981
163.61-8(1)	Color	Yes	Tech. Grade	No		Yes: October, 1981
163.61-8(2)	Odor	Yes	Tech. Grade	No		Yes: October, 1981
163.61-8(3)	Melting Point	Yes	Tech. Grade	No		Yes: October, 1981
163.61-8(4)	Solubility	Yes	Tech. Grade	No		Yes: October, 1981
163.61-8(5)	Stability	Yes	Tech. Grade	No		Yes: October, 1981
163.61-8(6)	Octanol/Water Partition Coefficient	Yes	Tech. Grade	No		Yes: October, 1981
163.61-8(7)	Physical State	Yes	Tech. Grade	Yes		
163.61-8(8)	Density or Specific Gravity	Yes	Tech. Grade	No		Yes: October, 1981
163.61-8(9)	Boiling Point	No				
163.61-8(10)	Vapor Pressure	Yes	Tech. Grade	No		Yes: October, 1981
163.61-8(11)	pH	Yes	Tech. Grade	No		Yes: October, 1981

* Technical Grade Ammonium and Monomethyl Ammonium Chloramben

These data requirements are current as of May, 1981. Refer to guidance package for updated requirements.

TABLE-3-3 (con)

GENERIC DATA REQUIREMENTS AND DATA GAPS
FOR END-USE PRODUCTS CONTAINING AMMONIUM CHLORAMBEN

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
TOXICOLOGY						
163.81-1	Acute Oral Toxicity	Yes	Ammonium & Monomethyl ammonium*	No		Yes: October, 1981
163.81-2	Acute Dermal Toxicity	Yes	Ammonium & Monomethyl ammonium*	No		Yes: October, 1981

* Data on technical grade ammonium and monomethyl ammonium chloramben are required. Acute oral and dermal toxicity testing on technical grade sodium chloramben (or chloramben) will not satisfy this requirement.

These data requirements are current as of May, 1981. Refer to guidance package package for updated requirements.

TABLE-3-4

PRODUCT-SPECIFIC DATA REQUIREMENTS AND DATA GAPS FOR SOLUBLE CONCENTRATE CHLORAMBEN PRODUCTS

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?*	Bibliographic Citation	Must Additional Data Be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
PRODUCT CHEMISTRY						
163.61-6	Declaration of Ingredient Limits	Yes	Each S.C. Product	No		Yes: October, 1981
163.61-7	Product Analyt. Methods and Data	Yes	Each S.C. Product	Partial: Need Data		Yes: October, 1981
163.61-8(1)	Color	Yes	Each S.C. Product	No		Yes: October, 1981
163.61-8(2)	Odor	Yes	Each S.C. Product	No		Yes: October, 1981
163.61-8(7)	Physical State	Yes	Each S.C. Product	Yes		
163.61-8(8)	Density or Specific Gravity	Yes	SC***	No		Yes: October, 1981
163.61-8(9)	Boiling Point	Yes	SC***	No		Yes: October, 1981
163.61-8(10)	Vapor Pressure	Yes	SC**	No		Yes: October, 1981
163.61-8(11)	pH	Yes	SC***	No		Yes: October, 1981
163.61-8(12)	Storage Stab.	Yes	SC***	No		Yes: October, 1981
163.61-8(13)	Flammability	Yes	SC***	No		Yes: October, 1981
163.61-8(14)	Oxidizing or Reducing Action	Yes	SC***	No		Yes: October, 1981
163.61-8(15)	Explosiveness	Yes	SC***	No		Yes: October, 1981
163.61-8(16)	Miscibility	Yes	SC***	No		Yes: October, 1981
163.61-8(17)	Viscosity	Yes	SC***	No		Yes: October, 1981
163.61-8(18)	Corrosion Characteristics	Yes	SC***	No		Yes: October, 1981

* For Currently Registered Products

** Each Soluble Concentrate Product

*** Each Soluble Concentrate Product or Substantially Similar Product

These data requirements are current as of May, 1981. Refer to guidance package for updated requirements.

TABLE 3-4 (con)

PRODUCT-SPECIFIC DATA REQUIREMENTS AND DATA GAPS
FOR SOLUBLE CONCENTRATE CHLORAMBEN PRODUCTS

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?*	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
TOXICOLOGY						
163.81-1	Acute Oral Toxicity	Yes	SC**	Partial: Need product purity for 0001, 0024	Biosearch, 1969, 0001 Hazleton, 1966, 0024	Yes: October, 1981
163.81-2	Acute Dermal Toxicity	Yes	SC**	No: Ammonium Chloramben Partial: Amm. & Monomethyl ammonium, need product purity for 0002	Biosearch, 1969, 0002	Yes: October, 1981
163.81-3	Acute Inhal. Toxicity	Yes	SC**	No		Yes: October, 1981
163.81-4	Prim. Eye Irritation	Yes	SC**	No: Ammonium Chloramben Partial: Amm. & Monomethyl ammonium, need product purity for 0003	Biosearch, 1969, 0003	Yes: October, 1981
163.81-5	Primary Dermal Irritation	Yes	SC**	No: Ammonium Chloramben Partial: Amm. & Monomethyl ammonium, need product purity for 0002	Biosearch, 1969, 0002	Yes: October, 1981

* For Currently Registered Products

** Each Soluble Concentrate Product or Substantially Similar Product. Currently Registered Products Containing Ammonium Chloramben Have Been Determined to be Substantially Similar, and Currently Registered Products Containing Ammonium Chloramben and Monomethylammonium Chloramben are Substantially Similar. Required testing is to be completed on Formulations containing 23.4% Ammonium Chloramben AND 15.7% Ammonium Chloramben & 47.2% Monomethyl-ammonium Chloramben should be tested.

These data requirements are current as of May, 1981. Refer to guidance package for updated requirements.

TABLE-3-5

PRODUCT-SPECIFIC DATA REQUIREMENTS AND DATA GAPS FOR FLOWABLE CONCENTRATE CHLORAMBEN PRODUCTS

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?*	Bibliographic Citation	Must Additional Data Be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
PRODUCT CHEMISTRY						
163.61-6	Declaration of Ingredient Limits	Yes	Each F.C. Product**	No		Yes: October, 1981
163.61-7	Product Analyt. Methods and Data	Yes	Each F.C. Product**	Partial: Need Data		Yes: October, 1981
163.61-8(1)	Color	Yes	Each F.C. Product**	No		Yes: October, 1981
163.61-8(2)	Odor	Yes	Each F.C. Product**	No		Yes: October, 1981
163.61-8(7)	Physical State	Yes	Each F.C. Product**	Yes		
163.61-8(8)	Density or Specific Gravity	Yes	FC***	No		Yes: October, 1981
163.61-8(9)	Boiling Point	Yes	FC***	No		Yes: October, 1981
163.61-8(10)	Vapor Pressure	Yes	FC**	No		Yes: October, 1981
163.61-8(11)	pH	Yes	FC***	No		Yes: October, 1981
163.61-8(12)	Storage Stab.	Yes	FC***	No		Yes: October, 1981
163.61-8(13)	Flammability	Yes	FC***	No		Yes: October, 1981
163.61-8(14)	Oxidizing or Reducing Action	Yes	FC***	No		Yes: October, 1981
163.61-8(15)	Explosiveness	Yes	FC***	No		Yes: October, 1981
163.61-8(16)	Miscibility	Yes	FC***	No		Yes: October, 1981
163.61-8(17)	Viscosity	Yes	FC***	No		Yes: October, 1981
163.61-8(18)	Corrosion Characteristics	Yes	FC***	No		Yes: October, 1981

* For Currently Registered Products

** Each Flowable Concentrate Product

*** Each Flowable Concentrate Product or Substantially Similar Product

These data requirements are current as of May 1981. Refer to guidance package for updated requirements.

TABLE-3-5 (con)

PRODUCT-SPECIFIC DATA REQUIREMENTS AND DATA GAPS
FOR FLOWABLE CONCENTRATE CHLORAMBEN PRODUCTS

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?*	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
TOXICOLOGY						
163.81-1	Acute Oral Toxicity	Yes	FC**	Yes	Hazleton, 1959, 0022	No
163.81-2	Acute Dermal Toxicity	Yes	FC**	Yes	Hazleton, 1959, 0023 CDC Res., 1978, 0065	No
163.81-3	Acute Inhal. Toxicity	Yes	FC**	Yes	Food & Drug, 1978, 0062	No
163.81-4	Prim. Eye Irritation	Yes	FC**	Yes	CDC Res., 1978, 0064	No
163.81-5	Primary Dermal Irritation	Yes	FC**	Yes	CDC Res., 1978, 0063	No

* For Currently Registered Products

** Each Flowable Concentrate Product or Substantially Similar Product. Currently Registered Products Containing Sodium Chloramben Have Been Determined to be Substantially Similar. Testing is to be completed on Formulations containing Sodium Chloramben or Technical Chloramben Acid.

These data requirements are current as of May, 1981. Refer to guidance package for updated requirements.

TABLE-3-6

PRODUCT-SPECIFIC DATA REQUIREMENTS AND DATA GAPS FOR EMULSIFIABLE CONCENTRATE CHLORAMBEN PRODUCTS

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?*	Bibliographic Citation	Must Additional Data Be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
PRODUCT CHEMISTRY						
163.61-6	Declaration of Ingredient Limits	Yes	Each E.C. Product**	No		Yes: October, 1981
163.61-7	Product Analyt. Methods and Data	Yes	Each E.C. Product**	No		Yes: October, 1981
163.61-8(1)	Color	Yes	Each E.C. Product**	No		Yes: October, 1981
163.61-8(2)	Odor	Yes	Each E.C. Product**	No		Yes: October, 1981
163.61-8(7)	Physical State	Yes	Each E.C. Product**	Yes		
163.61-8(8)	Density or Specific Gravity	Yes	EC***	No		Yes: October, 1981
163.61-8(9)	Boiling Point	Yes	EC***	No		Yes: October, 1981
163.61-8(10)	Vapor Pressure	Yes	EC**	No		Yes: October, 1981
163.61-8(11)	pH	Yes	EC***	No		Yes: October, 1981
163.61-8(12)	Storage Stab.	Yes	EC***	No		Yes: October, 1981
163.61-8(13)	Flammability	Yes	EC***	No		Yes: October, 1981
163.61-8(14)	Oxidizing or Reducing Action	Yes	EC***	No		Yes: October, 1981
163.61-8(15)	Explosiveness	Yes	EC***	No		Yes: October, 1981
163.61-8(16)	Miscibility	Yes	EC***	No		Yes: October, 1981
163.61-8(17)	Viscosity	Yes	EC***	No		Yes: October, 1981
163.61-8(18)	Corrosion Characteristics	Yes	EC***	No		Yes: October, 1981

* For Currently Registered Product
** Each Emulsifiable Concentrate Product
*** Each Emulsifiable Concentrate Product or Substantially Similar Product

These data requirements are current as of May, 1981. Refer to guidance package for updated requirements.

TABLE-3-6 (con)

PRODUCT-SPECIFIC DATA REQUIREMENTS AND DATA GAPS
FOR EMULSIFIABLE CONCENTRATE CHLORAMBEN PRODUCTS

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?*	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
TOXICOLOGY						
163.81-1	Acute Oral Toxicity	Yes	EC**	Partial: Need product purity for 0024	Hazleton, 1966, 0024	Yes: October, 1981
163.81-2	Acute Dermal Toxicity	Yes	EC**	Partial: Need Product purity for 0143	Hazleton, 1968, 0143	Yes: October, 1981
163.81-3	Acute Inhal. Toxicity	Yes	EC**	Partial: Need product purity for 0144	Hazleton, 1968, 0144	Yes: October, 1981
163.81-4	Prim. Eye Irritation	Yes	EC**	Partial: Need product purity for 0143	Hazleton, 1968, 0143	Yes: October, 1981
163.81-5	Primary Dermal Irritation	Yes	EC**	No		Yes: October, 1981

These data requirements are current as of May, 1981. Refer to guidance package to updated requirements.

* For Currently Registered Product.

** Each Emulsifiable Concentrate Product or Substantially Similar Product.

TABLE-3-7

PRODUCT-SPECIFIC DATA REQUIREMENTS AND DATA GAPS
FOR GRANULAR CHLORAMBEN PRODUCTS

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?*	Bibliographic Citation	Must Additional Data Be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
PRODUCT CHEMISTRY						
163.61-6	Declaration of Ingredient Limits	Yes	Each GR. Product	No		Yes: October, 1981
163.61-7	Product Analyt. Methods and Data	Yes	Each GR. Product	No		Yes: October, 1981
163.61-8(1)	Color	Yes	Each GR. Product	No		Yes: October, 1981
163.61-8(2)	Odor	Yes	Each GR. Product	No		Yes: October, 1981
163.61-8(7)	Physical State	Yes	Each GR. Product	Yes		
163.61-8(8)	Density or Specific Gravity	Yes	GR***	No		Yes: October, 1981
163.61-8(9)	Boiling Point	No				
163.61-8(10)	Vapor Pressure	Yes	GR***	No		Yes: October, 1981
163.61-8(11)	pH	Yes	GR***	No		Yes: October, 1981
163.61-8(12)	Storage Stab.	Yes	GR***	No		Yes: October, 1981
163.61-8(13)	Flammability	Yes	GR***	No		Yes: October, 1981
163.61-8(14)	Oxidizing or Reducing Action	Yes	GR***	No		Yes: October, 1981
163.61-8(15)	Explosiveness	Yes	GR***	No		Yes: October, 1981
163.61-8(16)	Miscibility	Yes	GR***	No		Yes: October, 1981
163.61-8(17)	Viscosity	Yes	GR***	No		Yes: October, 1981
163.61-8(18)	Corrosion Characteristics	Yes	GR***	No		Yes: October, 1981

* For Currently Registered Products
** Each Granular Product
*** Each Granular Product or Substantially Similar Product.

These data requirements are current as of May, 1981. Refer to guidance package for updated requirements.

TABLE-3-7 (con)

PRODUCT-SPECIFIC DATA REQUIREMENTS AND DATA GAPS
FOR GRANULAR CHLORAMBEN PRODUCTS

Guideline Citation	Name of Test	Are Data Required?	Test Substance	Does EPA Have Data to Partially or Totally Satisfy Requirement?*	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, deadline for submission.
TOXICOLOGY						
163.81-1	Acute Oral Toxicity	Yes	GR**	Partial: product purity for 0001, 0024	Biosearch, 1969, 0001 Hazleton, 1966, 0024	Yes: October, 1981
163.81-2	Acute Dermal Toxicity	Yes	GR**	No: Ammonium Partial: Amm. & Monomethyl ammon., need product purity for 0002	Biosearch, 1969,0002	Yes: October, 1981
163.81-3	Acute Inhal. Toxicity	Yes	GR**	No		Yes: October, 1981
163.81-4	Prim. Eye Irritation	Yes	GR**	No: Ammonium Partial: Amm. & Monomethyl ammon., need product purity for 0003	Biosearch, 1969,0003	Yes: October, 1981
163.81-5	Prim. Dermal Irritation	Yes	GR**	No: Ammonium Partial: Amm. & Monomethyl ammon., need product purity for 0002	Biosearch, 1969, 0002	Yes: October, 1981

* For Currently Registered Products

** Each Granular Product or Substantially Similar Product.
Currently Registered Products Containing Ammonium Chloramben Have Been Determined to be Substantially Similar, and Currently Registered Products Containing Ammonium Chloramben and Monomethylammonium Chloramben are Substantially Similar. Testing is to be completed on Formulations containing 23.4% Ammonium Chloramben AND 15.7% Ammonium Chloramben & 47.2% Monomethyl-ammonium Chloramben should be tested.

These data requirements are current as of May, 1981. Refer to guidance package for updated requirements.

CHAPTER IV

PRODUCT CHEMISTRY

A. Introduction

FIFRA 3(c)(2)(A) requires the Agency to establish guidelines for registering pesticides in the United States. The Proposed Guidelines require registrants to provide quantitative data on all added ingredients, active and inert, which are equal to or greater than 0.1 percent of the product by weight.

To establish the composition of products proposed for registration, the Agency requires data and information not only on the manufacturing and formulation processes but also a discussion on the formation of manufacturing impurities and other product ingredients, intentional and unintentional. Further, to assure that the composition of the product as marketed will not vary from the composition evaluated at the time of registration, applicants are required to submit a statement certifying upper and lower composition limits for the active and inert ingredients, or upper limits only for some unintentional ingredients. Subpart D of the Proposed Guidelines (40 FR 29696, July 10, 1978) suggests specific precision limits for ingredients based on the percentage of ingredients and the standard deviation of the analytical method.

In addition to the data on product composition, the Agency guidelines also require data to establish the physical and chemical properties of both the herbicidal active ingredient and its formulations. For example, data are needed concerning the identity and physical state of the active ingredient (e.g., flammability, corrosiveness or storage stability). The Agency uses these data to characterize each herbicide and to determine its environmental and health hazards.

B. Chloramben Manufacturing-Use Products

1. Product Chemistry Profile

Technical grade chloramben is 3-amino 2,5-dichlorobenzoic acid.

Two manufacturing-use products are currently registered. These are the sodium salt of chloramben and the methyl ester of chloramben.

Some data are available on the physical and chemical properties of technical grade chloramben. (Amchem, 196?, 0081; Amchem, 1959, 0124; Amchem, 1960, 0125). It is a white crystalline powder, melting at about 195°C. (The pure material melts at 201°C.) It has an aqueous solubility of 700 ppm, and is easily soluble in ethanol (17.3 g/100 ml). It is 50 percent ionized at a pH of 5.6.

Sodium chloramben is a crystalline powder with a bulk density about three quarters that of water. It is very soluble in water and insoluble in aromatic solvents. It has no known oxidizing or reducing action. (Amchem, 1974, 0054)

Methyl chloramben is a crystalline solid only slightly soluble in water (120 ppm) and soluble in organic solvents (alcohol, acetone, ether, and aromatic solvents). (Amchem, 1966, 0037)

Methods for the determination of chloramben in the technical grade chemical have been submitted to the Agency (Amchem, 1979, 0054; Amchem, 197?, 0083). Although these methods are old, they seem adequate for quality control and enforcement purposes.

Analytical methods have been supplied both for the assay of manufacturing-use and formulated products, and for the determination of isomers of chloramben in low concentration (Amchem, 1979, 0054; Amchem, 197?, 0083). These methods also are adequate for quality control and enforcement purposes.

2. Data Requirements and Data Gaps

Listed below are the Product chemistry data needed to support adequately the registration of manufacturing-use chloramben products. Preceding each data requirement is the section of the proposed guidelines for the registration of pesticides in the United States (43 FR 29696 July 10, 1978) which describes the type of data required. Applicants for registration must submit or cite the following information, which either has not yet been submitted to the Agency, or is insufficient to satisfy the requirements.

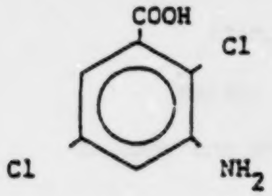
	Data Requirement	Technical Chloramben Acid	Manufacturing-Use Chloramben Sodium	Methyl
163.61-3	Identification of product and disclosure of ingredients			
163.61-4(a)	Composition of starting and intermediate materials in manufacturing process	X	X	X
163.61-4(b)	Detailed manufacturing process		X	X
163.61-5	Discussion on formation of unintentional ingredients		X	X
163.61-6(a)	Declaration of Limits			X
163.61-6(b)	Certification of Limits		X	X
163.61-7	Analytical methods and results	X (results)	X (results)	X
163.61-8(c)	Physical and Chemical properties			
	color		X	
	odor	X		
	stability	X		
	octanol/water partition coefficient	X		
	density	X		X
	vapor pressure	X		X
	pH	X	X	X
	storage stability		X	X
	flammability		X	X
	oxidizing or reducing action			X
	explosiveness			X
	miscibility			X
	viscosity			X
	corrosion characteristics		X	X

3. Topical Discussions

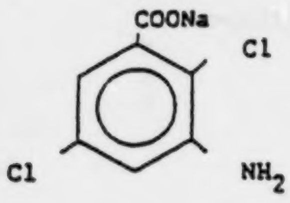
a. Chemical Identity

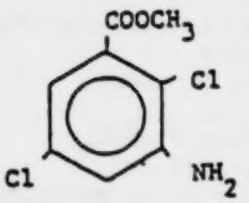
The Proposed Guidelines require identifying information including chemical names, product names, and numerical codes of all substances known or assumed to be present in pesticide products. (163.61-3)

"Chloramben" is the common name accepted by the American National Standards Institute (ANSI) for the chemical 3-amino 2,5-dichlorobenzoic acid. Chloramben is also known by the trade names Amiben, Vegiben, and Weedone. The common name will be used throughout this Standard in lieu of other chemical or trade names. The Chemical Abstracts number is 133-90-4, the EPA Shaughnessy code is 029901 and the molecular formula is $C_6H_2Cl_2(NH_2)COOH$. It has the following structure:



The following structures represent respectively sodium chloramben (Chemical Abstracts number 1954-81-0) and methyl chloramben (Chemical Abstracts number 7286-84-2):





These are similar to chloramben itself except that the carboxylic acid hydrogen has been replaced by sodium or by the methyl group.

b. Manufacturing Processes

Because the route by which a pesticide is synthesized determines the nature and amount of potentially toxic impurities, a detailed description of the manufacturing process is required (163.61-4).

The details of the process which have been submitted are lacking in many details, including concentrations, equipment used, the process solvents, the reaction conditions (including temperatures and periods of time for elevated temperatures), purification steps, quality control measures, an indication of whether batch or continuous process is used, and a description of materials used for packaging. The confidential appendix to this document contains the submitted information on the manufacturing processes. This information is not sufficiently detailed, and does not provide sufficient data to fulfill requirements.

c. Formation of Unintentional Ingredients

Section 163.61-5 of the Proposed Guidelines requires registrants of technical grade, manufacturing-use, and formulated products to submit a theoretical discussion of the formation of unintended substances in the product.

Available data on known impurities in chloramben manufacturing-use products are summarized in the confidential discussion appendix to this document. A discussion of the formation of these impurities in sodium and methyl chloramben manufacturing-use products is required.

Use of the specific nitrosamine detector in the analysis of "Amiben" (Amchem, 1978, 0153) indicates that nitrosamines are not present in this formulation. The level of detection was .05 ppm. Available information on the manufacturing process does not cause suspicions of nitrosamine formation. Additional data are not required on nitrosamines.

d. Ingredient Limits in Pesticide Products

The Guidelines require that upper and lower limits be established for each active ingredient and each intentionally added inert in a pesticide product (163.61-6). The two manufacturing-use chloramben products contain approximately 90 percent of chloramben acid equivalent in both cases. Upper and lower limits have not been established and certified for manufacturing-use methyl chloramben.

e. Analytical Methods and Data

The Guidelines require submission of, or reference to, analytical methods for measuring each active ingredient and each identifiable impurity in a pesticide product (163.61-7).

Section 163.61-7 of the Proposed Guidelines also require that applications for registration of pesticide products contain analytical data obtained by methods supplied to the Agency.

Acceptable methods for the determination of chloramben and some impurities in manufacturing-use chloramben are contained in the confidental discussion appendix. Data obtained by the method are not available.

f. Physical and Chemical Properties

For every pesticide product, the Proposed Guidelines require data on certain physical and chemical properties useful for identification purposes or for evaluation of hazard potential (163.61-8).

A small amount of data are available on the physical and chemical properties of chloramben acid, sodium chloramben, and methyl chloramben. An outline of the properties of chloramben acid, sodium chloramben, and methyl chloramben was given in the product chemistry profile earlier in this chapter. Some additional details on these compounds follows:

Chloramben (Amchem, 196?, 0081; Amchem, 1959, 0124; Amchem, 1960, 0125)

Color: White
Melting Point: 200-201°C
Physical State: Crystalline solid
Stability: Stable towards oxidation and heat under conventional conditions
Solubility: Water, .07g/100g; ethanol, 17.3g/100g
Vapor Pressure: .0007 mm Hg at 100°

Sodium chloramben: (Amchem, 1979, 0054; Amchem, 1979 jacket 264-306)

Color: Conflicting data submitted
Melting Point: 271°C ,
Physical State: Crystalline solid, described as granular hollow sphere
Stability: Temperature stable at least up to the melting point.
Solubility: Very easily soluble in water, insoluble in aromatic solvents

Methyl chloramben: (Amchem, 1966, 0037)

Color: Off white
Melting Point: 63-64°C
Physical State: Crystalline solid
Stability: Temperature stable at least up to the melting point. Stable under GC conditions.
Solubility: Water, 120 ppm; soluble in aromatic solvents (alcohol, acetone, ether, aromatic solvents)

C. Soluble Concentrate Chloramben

In this category there are two basic configurations or formulations of chloramben. First, there is a formulation in which the ammonium salt of chloramben is the sole active ingredient at a concentration of 23.4 percent. There is a second formulation in which ammonium chloramben (15.7 percent) and the monomethyl ammonium salt (47.2 percent) of chloramben are both ingredients.

These end-use products are produced by an integrated formulation system. Product chemistry data are required on technical grade ammonium and monomethyl ammonium chloramben, as well as on specific end-use products.

No physical or chemical properties were disclosed for ammonium or monomethyl ammonium chloramben or any end-use formulations.

1. Data Gaps

Data needed on technical grade ammonium and monomethyl ammonium chloramben in soluble concentrate products:

1) Identification....................................163.61-3(b)
2) Composition of material.........................163.61-3(c)
3) Analytical methods and data....................163.61-7
4) Physical and chemical properties
    - a. Color (monomethyl ammonium chloramben).....163.61-8(c)(1)
    - b. Odor...163.61-8(c)(2)
    - c. Melting point.................................163.61-8(c)(3)
    - d. Solubility.....................................163.61-8(c)(4)
    - e. Stability......................................163.61-8(c)(5)
    - f. Octanol/Water particion coefficient........163.61-8(c)(6)
    - g. Physical state...............................163.61-8(c)(7)
    - h. Specific gravity or density.................163.61-8(c)(8)
    - i. Boiling point.................................163.61-8(c)(9)
    - j. Vapor pressure...............................163.61-8(c)(10)
    - k. pH...163.61-8(c)(11)

Data needed on soluble concentrate end-use products:

1) Declaration and certification of limits......163.61-6
2) Analytical methods and data...................163.61-7
3) Physical and chemical properties
    - a. Color...163.61-8(c)(1)
    - b. Odor..163.61-8(c)(2)
    - c. Density or Specific Gravity..............163.61-8(c)(8)
    - d. Boiling Point................................163.61-8(c)(9)
    - e. Vapor Pressure..............................163.61-8(c)(10)
    - f. pH..163.61-8(c)(11)
    - g. Storage Stability...........................163.61-8(c)(12)
    - h. Flammability.................................163.61-8(c)(13)
    - i. Oxidizing or Reducing Action.............163.61-8(c)(14)
    - j. Explosiveness................................163.61-8(c)(15)
    - k. Miscibility...................................163.61-8(c)(16)
    - l. Viscosity......................................163.61-8(c)(17)
    - m. Corrosion Characteristics.................163.61-8(c)(18)

2. Topical Discussions

The Agency has not received acceptable product chemistry data for any soluble concentrate chloramben product nor for technical grade ammonium chloramben or monomethyl ammonium chloramben.

The following are data required of all soluble concentrate formulated products of chloramben.

a. Chemical Identity and Disclosure of Ingredients

The proposed Guidelines require that the technical grade of each active ingredient in a formulated product be identified by name and by statement of formula identifying each reasonably identifiable substance in the technical grade chemical. Each of these substances shall be listed as a percentage or as ppm (by weight) of the technical chemical used in the product.

Data on technical grade ammonium and technical grade monomethyl ammonium chloramben have not been submitted in sufficient detail.

In addition, the proposed Guidelines require that applications for registration of a formulated product shall contain identifying information on each substance known to be present in the product, and those reaction products and degradation products known or theorized to be formed in the pesticide product during its manufacture or during its marketable life.

Insufficient data have been submitted.

b. Active Ingredient Limits

For all pesticides, the Guidelines require that the upper and lower limits be established for each active and inert ingredient, and upper limits for each possible reaction product and degradation product (163.61-6). Current registrations of soluble concentrate chloramben contain 23.4 percent ammonium chloramben in the case where ammonium chloramben is the sole active ingredient and 15.7 percent ammonium chloramben and 47.2 percent monomethyl ammonium chloramben in the case where the two salts are mixed.

For neither soluble concentrate formulation of chloramben has an upper and lower active ingredient limit been established for possible reaction products or degradation products.

c. Analytical Methods and Data

The Guidelines would require submission of, or reference to, analytical methods measuring each active ingredient in a pesticide product (163.61-7). Methods for the determination of total anionic amino compound present and for the determination of chloramben and its isomers have been submitted (Amchem, 1979, 0054; Amchem, 197?, 0083). The determination is done in two steps. First, all amino compounds are determined via diazometric titration. The chloramben itself is determined by methylating the carboxylic acid group and determining the methyl ester concentration via gas chromatography. In this method the methyl 3-amino 2,5-dichlorobenzoate is separated by the gas chromatographic technique from other related amino compounds (most of which are related aminodichlorobenzoic esters) and determined as a pure isomer.

Section 163.61-7 of the Proposed Guidelines requires that applicants for registration of pesticide products submit analytical data obtained by methods supplied to the Agency. Data obtained by the method described above have not been submitted for soluble concentrate products.

Section 163.61-7 of the Proposed Guidelines would also require that registrants of the formulated products produced by the integrated formulation system (Proposed Guidelines Section 163.61-1) submit methods not only for the active ingredient but for each identifiable impurity associated with manufacture of the technical chemical. Since the active ingredients (ammonium and monomethyl ammonium chloramben) in soluble concentrate products are not registered manufacturing-use products, the manufacturing process for these products is an integrated formulation system. Analytical methods, and data obtained from these methods are required for each identifiable impurity.

Such methods and data have not been submitted for any chloramben formulation.

d. Physical and Chemical Properties

For every pesticide product the Proposed Guidelines would require data on certain physical and chemical properties useful for identification purposes or for evaluation of hazard potential. (163.61-8)

There are no data available except for the off-white color of ammonium chloramben.

D. Flowable Concentrate Chloramben

In this category are formulations of sodium chloramben (a registered manufacturing-use chemical) as the sole active ingredient. The two registered formulations contain 83 and 21 percent sodium chloramben, respectively.

1. Data Gaps

1)	Declaration and certification of limits	163.61-6
2)	Data from analytical methods	163.61-7
3)	Physical and chemical properties	
a.	Color	163.61-8(c)(1)
b.	Odor	163.61-8(c)(2)
c.	Density or Specific Gravity	163.81-8(c)(8)
d.	Boiling Point	163.61-8(c)(9)
e.	Vapor Pressure	163.61-8(c)(10)
f.	pH	163.61-8(c)(11)
g.	Storage Stability	163.61-8(c)(12)
h.	Flammability	163.61-8(c)(13)
i.	Oxidizing or Reducing Action	163.61-8(c)(14)
j.	Explosiveness	163.61-8(c)(15)
k.	Corrosion Characteristics	163.61-8(c)(18)

2. Topical Discussions

The product chemistry of sodium chloramben per se has been dealt with under Manufacturing-use Products.

a. Ingredient Limits in Pesticide Products

For all pesticide products, the Guidelines would require that upper and lower limits be established for each active and inert ingredient, and upper limits for each impurity, reaction product, and degradation product (163.61-6).

For no flowable concentrate formulation of chloramben have limits been established for impurities, reactions products or degradation products.

b. Analytical Methods and Data

The Guidelines would require submission of, or reference to, analytical methods measuring each active ingredient in a herbicide product (163.61-7).

Methods for the determination of chloramben in flowable concentrate formulations have been submitted and are attached in the Confidential Appendix. These methods are similar to those outlined under Section C of this chapter for soluble concentrates of chloramben.

Section 163.61-7 of the Proposed Guidelines would require that applications for registration of pesticide products contain analytical data obtained by methods supplied to the Agency. Data obtained by the methods referred to above have not been submitted.

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c. Physical and Chemical Properties

For every pesticide product, the Proposed Guidelines require data on certain physical and chemical properties useful for identification purposes or for evaluation of hazard potential (163.61-8). None of the required data have been submitted.

E. Emulsifiable Concentrate Chloramben

There is one registered emulsifiable concentrate of chloramben. Methyl chloramben is contained as the sole active ingredient at 23.2 percent.

1. Data Gaps

1) Declaration and certification of limits..... 163.61-6
2) Analytical methods and data.................. 163.61-7
3) Physical and chemical properties
   - a. Color.................................. 163.61-8(c)(1)
   - b. Odor................................... 163.61-8(c)(2)
   - c. Density or Specific Gravity............ 163.81-8(c)(8)
   - d. Boiling Point.......................... 163.61-8(c)(9)
   - e. Vapor Pressure......................... 163.61-8(c)(10)
   - f. pH..................................... 163.61-8(c)(11)
   - g. Storage Stability...................... 163.61-8(c)(12)
   - h. Flammability........................... 163.61-8(c)(13)
   - i. Oxidizing or Reducing Action........... 163.61-8(c)(14)
   - j. Explosiveness.......................... 163.61-8(c)(15)
   - k. Corrosion Characteristics.............. 163.61-8(c)(18)

2. Topical Discussions

The product chemistry of methyl chloramben per se has been described previously, under Manufacturing-use products.

a. Ingredient Limits in Pesticide Products

For all pesticide products, the Guidelines would require that upper and lower limits be established for each active and inert ingredient, and upper limits for each impurity, reaction product, and degradation product (163.61-6).

Upper and lower limits have not been established for impurities, reaction products or degradation products in the currently registered emulsifiable concentrate product.

b. Analytical Methods and Data

The Guidelines would require submission of, or reference to, analytical methods measuring each active ingredient in a herbicide product (163.61-7).

Methods for the determination of chloramben in soluble concentrate formulations have been submitted and are attached in the confidential appendix. These methods are not readily adaptable to the analysis of chloramben in emulsifiable concentrate formulations, and hence the lack of a suitable analytical method is identified as a data gap.

Section 163.61-7 of the Proposed Guidelines would require that applications for registration of pesticide products contain analytical data obtained by methods supplied to the Agency. No such data have been submitted.

c. Physical and Chemical Properties

For every pesticide product, the Proposed Guidelines require data on certain physical and chemical properties useful for identification purposes or for evaluation of hazard potential (163.61-8). None of the required data has been submitted.

F. Granular Chloramben

Granular chloramben exists in two different forms. The first is granular chloramben where the sole active ingredient is ammonium chloramben. This exists in formulations of 1.3 percent, 4.3 percent and 10.8 percent ammonium chloramben. The second formulation is one in which ammonium chloramben is mixed with monomethyl ammonium chloramben. This exists in two different concentrations. One is 5.4 percent ammonium chloramben plus 17.3 percent monomethyl ammonium chloramben. The other is 2.82 percent ammonium chloramben and 8.46 percent monomethyl ammonium chloramben.

Granular chloramben products, like soluble concentrate chloramben products, are produced by integrated formulation systems. Consequently, product chemistry data are required on the technical grade ammonium and monomethyl ammonium chloramben in addition to data on specific end-use products.

1. Data Gaps

Data needed on technical grade ammonium and monomethyl ammonium chloramben:

1) Identification	163.61-3(b)
2) Composition of material	163.61-3(c)
3) Analytical methods and data	163.61-7
4) Physical and chemical properties	
a. Color (monomethyl ammonium chloramben)	163.61-8(c)(1)
b. Odor	163.61-8(c)(2)
c. Melting point	163.61-8(c)(3)
d. Solubility	163.61-8(c)(4)
e. Stability	163.61-8(c)(5)
f. Octanol/Water particion coefficient	163.61-8(c)(6)
g. Physical state	163.61-8(c)(7)
h. Specific gravity or density	163.61-8(c)(8)
i. Boiling point	163.61-8(c)(9)
j. Vapor pressure	163.61-8(c)(10)
k. pH	163.61-8(c)(11)

Data needed on granular end-use products:

1) Declaration and certification of limits	163.61-6
2) Analytical methods and data	163.61-7
3) Physical and chemical properties	
a. Color	163.61-8(c)(1)
b. Odor	163.61-8(c)(2)
c. Density or Specific Gravity	163.61-8(c)(8)
d. Boiling Point	163.61-8(c)(9)
e. Vapor Pressure	163.61-8(c)(10)
f. pH	163.61-8(c)(11)
g. Storage Stability	163.61-8(c)(12)
h. Flammability	163.61-8(c)(13)
i. Oxidizing or Reducing Action	163.61-8(c)(14)
j. Explosiveness	163.61-8(c)(15)
k. Miscibility	163.61-8(c)(16)
l. Viscosity	163.61-8(c)(17)
m. Corrosion Characteristics	163.61-8(c)(18)

2. Topical Discussions

The Agency has not received acceptable product chemistry data for any granular chloramben product. No data on technical grade ammonium or monomethyl ammonium chloramben have been submitted.

a. Chemical Identity and Disclosure of Ingredients

The proposed Guidelines require that the technical grade of each active ingredient in a formulated product be identified by name and by statement of formula identifying each reasonably identifiable substance in the technical grade chemical. Each of these substances shall be listed as a percentage or as ppm (by weight) of the technical chemical used in the product.

Data on technical grade ammonium and monomethyl ammonium chloramben have not been submitted in sufficient detail.

In addition, the proposed Guidelines require that applications for registration of a formulated product shall contain identifying information on each substance known to be present in the product, and those reaction products and degradation products known or theorized to be formed in the pesticide product during its manufacture or during its marketable life.

Insufficient data have been submitted.

b. Active Ingredient Limits in Pesticide Products

For all pesticide products, the Guidelines would require that upper and lower limits be established for each active and inert ingredient, and upper limits for each impurity, reaction product, and degradation product (163.61-5).

For no granular formulation of chloramben has an upper and lower limit been established.

c. Analytical Methods and Data

The Guidelines would require submission of, or reference to, analytical methods measuring each active ingredient in a herbicide product (163.61-7). Methods for the determination of chloramben in soluble concentrate formulations have been submitted, as previously discussed. It is felt that these methods may not be suitable for the determination of chloramben in granular formulations because the prescence of large quantities of solid inerts, which are likely to have adsorptive properties, make uncertain recoveries of chloramben from granular formulations.

Section 163.61-7 of the Proposed Guidelines would require that applications for registration of pesticide products contain analytical data obtained by methods supplied to the Agency. Such analytical data have not been submitted.

Section 163.61-7 of the Proposed Guidelines would also require that registrants of formulated products produced by an integrated formulation system (Proposed Guidelines, Section 163.61-1) submit methods not only for the active ingredient, but for each identifiable impurity associated with manufacture of the technical chemical. Such methods have not been submitted for any chloramben formulation. Since the active ingredients (ammonium and monomethyl ammonium chloramben) in granular chloramben products are not registered manufacturing-use products, the manufacturing process for these products is an integrated formulation system. Analytical methods and data obtained through the use of these methods are required for each identifiable impurity.

d. Physical and Chemical Properties

For every pesticide product, the Proposed Guidelines would require data on certain physical and chemical properties useful for identification purposes or for evaluation of hazard potential (163.61-8). None of the required data has been submitted.

CHAPTER V

ENVIRONMENTAL FATE OF CHLORAMBEN

A. Introduction

Data on the fate of a pesticide once it enters the environment are required to predict and estimate any potentially harmful effects on man and the environment. The fate of a pesticide depends on its formulation type, application methods or use patterns and its chemical, physical, and biological behavior in the environment.

Environmental studies from which data are required include physical and chemical degradation, metabolism, field dissipation, and accumulation.

Chloramben is available in four types of formulations: soluble concentrates, flowable concentrates, emulsifiable concentrates, and granulars. These formulations contain a variety of salts and esters of chloramben including sodium chloramben, methyl chloramben, ammonium chloramben, and monomethyl ammonium chloramben. Sodium chloramben and methyl chloramben are registered manufacturing-use products. The Agency has determined that data on the fate of chloramben in the environment are required on sodium and methyl chloramben. Data requested on sodium chloramben will support the registrations of products containing the sodium salt and products containing the ammonium and monomethyl ammonium salts.

B. Use Profile

The herbicide chloramben is used for the control of seedling annual grasses and seedling broadleaf weeds. The mechanism of action is the inhibition of root development in weed seedlings. The use of chloramben is principally pre-emergent, with some post-emergent use also.

Chloramben is registered for use in dry beans (white, navy, kidney, pinto, and lima), peanuts, soybeans, sunflowers, corn, sweet potatoes, squash, pumpkins, asparagus (seedling), transplanted tomatoes and peppers, snapbeans, lima beans, cantaloupes, cucumbers, annual and perennial flowers, shrubs, and trees.

Based on a preliminary quantitative usage analysis (PQUA) of chloramben prepared by Economic Analysis Branch (EAB), about 96 percent of the chloramben production is used on soybeans primarily in the north central states. This use represents approximately 7 percent of the total U.S. soybean acreage.

Of 24 federally registered products, Union Carbide Agricultural Products, Inc. is the major producer with seventeen registered products. There are four other registrants. Chloramben is registered as the ammonium salt, diethanolamine salt, sodium salt, monomethyl ammonium salt, and the methyl ester. Table 5-1 presents a complete listing of the chloramben federal registrations together with the form and concentration of the active ingredient(s). Chloramben is the sole active ingredient in 16 registrations. These 16 registrations include soluble concentrates, flowable concentrates, emulsifiable concentrates, and granular formulations. Not covered under this standard but included in Table 5-1 are eight registered mixtures of chloramben with other herbicides. Most of the registered products are designed for general agricultural use. However, one granular formulation, #264-191 is used primarily by homeowners. Table 5-2 gives the registered application rates of chloramben as indicated on product labels.

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TABLE 5-1

Chloramben Registrations[1]

Registration #	Form[2]	% Active Ingredient
264-138	SC	23.4% ammonium chloramben
264-167	G	10.8% ammonium chloramben
264-175	G	10.8% ammonium chloramben
264-178	SC	23.4% ammonium chloramben
264-191	G	1.3% ammonium chloramben
264-243	G	4.3% ammonium chloramben
264-251	G	5.4% ammonium chloramben plus 17.3% monomethylammonium chloramben
264-253	WP	27.7% sodium chloramben and 50.0% atrazine
264-254	WP	41.7% sodium chloramben and 12.5% linuron
264-256	EC	15.7% diethanolamine chloramben and 30.1% diethanolamine dinoseb
264-260	EC	23.2% methyl chloramben
264-266	SC	15.7% ammonium chloramben and 47.2% monomethylammonium chloramben
264-274	G	2.82% ammonium chloramben and 8.46% monomethylammonium chloramben
264-278	T	98.8% methyl chloramben
264-279	T	97.2% sodium chloramben
264-305	FC	83.0% sodium chloramben
264-306	FC	21.0% sodium chloramben
449-534	FC	17.5% ammonium chloramben 12.9% norea
635-630	G	5.4% ammonium chloramben and 4.0% norea

TABLE 5-1

Chloramben Registrations[1] - Continued

Registration #	Form[2]	% Active Ingredient
635-631	FC	17.5% ammonium chloramben and 12.9% norea
2749-160	G	10.8% ammonium chloramben
2749-202	SC	23.4% ammonium chloramben
43142-29	FC	17.5% ammonium chloramben and 12.9% norea
43142-30	G	5.4% ammonium chloramben and 4.0% norea

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1) Source for Table 5-1 was a PRD-1 printout dated June 12, 1980.
2) SC = Soluble Concentrate, G = Granular, WP = Wettable Powder, EC = Emulsifiable Concentrate, T = Technical, FC = Flowable Concentrate.

TABLE 5-2

REGISTERED APPLICATION RATES FOR CHLORAMBEN

Formulation Type	Site	Application Rate(1) (lb. a.i. per acre)
Soluble Concentrates		
23.4%-62.9%	Soybeans, dry beans, peanuts, sunflowers	2-3
	Corn	2
	Lima beans, squash, pumpkin	2-4
	Asparagus (seedling)	3
	Sweet potatoes	4
Flowable Concentrates		
21%-83%	Soybeans, dry beans, peanuts, sunflowers	2-3
	Lima beans, squash, pumpkin	2-4
	Asparagus (seedling)	3
	Sweet potatoes	4
Emulsifiable Concentrate		
23.2%	Snap beans, cantaloupes, cucumbers	2-3
Granular		
1.3%-22.7%	Soybeans, dry beans, peanuts, sunflowers	2-3
	Corn	2
	Sweet potatoes	4
	Ornamentals	4-6
	Transplanted tomatoes and peppers, lima beans, pumpkins, squash, asparagus (seedling)	4

(1) Where ranges are given, the higher rates are for heavy soils.

C. Manufacturing-Use Chloramben

1. Environmental Fate Profile

Sodium Chloramben

Sodium chloramben appears to be resistant to hydrolysis. This conclusion is, however, based on retention of phytotoxicity rather than actual field residue data. Limited studies indicate that there is no loss of phytotoxicity when aqueous solutions of chloramben are kept in the dark.

Photodegradation of sodium chloramben aqueous solutions appears to occur readily in sunlight. Total loss of phytotoxicity occurs in two days. Loss of phytotoxicity on dry soil is somewhat slower, being about 30 percent in 48 hours.

Soil bacteria bring about a loss of phytotoxicity in sodium chloramben after several weeks. It appears that this is due to a decarboxylation. The rate of reaction appears to be independent of soil pH within the range of 4.3 to 7.5.

Chloramben may have bactericidal properties towards Rhizobium japonicum. No other data are available on the effects of chloramben on other bacteria, nor on activated sludge.

The mobility of sodium chloramben is governed principally by its high solubility in water and its apparent limited strength of adsorption to soil particles. It appears to easily leach down in most soil types by rainfall. This factor, together with an apparent slow rate of bacterial degradation, indicates a potential for groundwater contamination.

Probably all plants grown in contact with sodium chloramben take up the compound. In some plants the subsequent movement of compound away from the roots is very slow, whereas in others it readily spreads throughout the plant. The fate of chloramben in plants includes decomposition, a detoxifying conjugation which proceeds fairly rapidly, or a detoxifying conjugation which goes slowly, if at all.

Methyl Chloramben

The methyl ester of chloramben acid appears to have the expected properties of a carboxylic acid ester. It is apparently not hydrolysed after a short period in contact with water at slightly acid pH values (5 to 6). Bacteria-mediated hydrolysis appears to be quick: approximately 50 percent of the ester is converted to the free acid in about one week when in contact with wet soil. A subsequent and slower bacteria reaction, shown by a loss of phytotoxicity, is probably a decarboxylation, as with sodium chloramben.

The leaching behavior of the methyl ester is governed by its aqueous solubility, which is much lower than that of the sodium salt (120 ppm and 250,000 ppm, respectively). For a given rainfall the ester seems to leach down about 15 percent of the distance travelled by the sodium salt.

2. Exposure Profile

Exposure to persons involved in the manufacture, handling, storage or shipment of technical or manufacturing-use grade chloramben is possible through four pathways; accidental ocular or dermal exposure, inhalation exposure, and repeated dermal exposure. Due to the scarcity of data on occupational exposure of these two grades of chloramben, it is impossible to quantitatively assess the human and wildlife exposure hazard.

There is little likelihood of oral and ocular exposure occurring unless by accident. the low volatility of flowable and soluble concentrates indicates that there is also little chance of inhalation exposure under normal circumstances. The granular chloramben may present a higher possibility of inhalation exposure to workers involved in bulk loading, unloading, and packaging of the substance. Due to its dry and solid physical state, the chances of it being inhaled in these work areas as an airborne particulate are moderately high.

In addition, repeated dermal exposure to all forms of manufacturing-use and technical grade chloramben present the highest exposure hazard. This may occur in the manufacturing and shipping phases of its production but the greatest repeated exposure is expected during bulk handling operations.

Should significant amounts of chloramben be spilled, drained, discharged or disposed of in the natural environment, aquatic life in waters affected by direct drainage or leaching are expected to receive high dosages of herbicide.

3. Data Requirements and Data Gaps

Not all the requirements of Section 163.62 (43 FR 29696, July 10, 1978) need to be fulfilled to support the registration of chloramben as a manufacturing-use product and as a formulated product, because the use pattern indicates that chloramben is unlikely to enter the environment in particular specified ways.

To support the registration of all chloramben products, it is necessary to submit or cite the following data tested on both sodium and methyl chloramben.

163.62-7	Physico-Chemical Degradation
	(b) Hydrolysis
	(c) Phytodegradation in water
	(c) Photodegradation in soil
163.62-8	Metabolism
	(b) Soil metabolism - aerobic
	(c) Soil metabolism - anaerobic
163.62-9	Mobility
	(b) Leaching
	(d) Adsorption/desorption
163.62-10	Field Dissipation
	(b) Terrestrial
163.62-11	Accumulation
	(b) Rotational crops
	(d) Fish accumulation

In addition to the above listed requirements, a field study measuring applicator exposure to liquid formulations of chloramben is required. The study should be conducted with a typical soluble or flowable concentrate formulation, which is mixed and then applied by ground equipment to a typical (160 acres) soybean field at recommended application rates. The Agency is requiring this study to verify the exposure estimates used in the oncogenic risk assessment.

Data Gaps

Although some data on the environmental fate of chloramben are currently available, none of the data requirements have been satisfied sufficiently with the exception of fish accumulation data on sodium chloramben.

4. Topical Discussions

Corresponding to each of the Topical Discussions listed below is the number of the section in the "Proposed Guidelines for Registering Pesticides in the United States" (43 FR 29696, July 10, 1978) which explains the minimum data that the Agency requires in order to adequately assess a pesticide's Environmental Fate.

All topics related to the Environmental Fate of chloramben as an active ingredient are discussed under Manufacturing-Use Chloramben.

a. Physico-Chemical Degradation 163.62-7

These studies should identify decomposition rates and pesticide residues which could adversely affect the environment. They include studies of the degradation of chloramben in the presence of water, and when subject to the action of light. Studies already carried out suggest that there are three pathways of degradation. One, the formation of free chloramben acid by ionization of the sodium salt or the breaking of the ester bond of methyl chloramben, results in a compound which is fully phytotoxic. A second pathway, a loss of the carboxylic acid group, probably occurs by the action of some bacteria, and results in an apparently non-phytotoxic compound. A third degradation pathway occurs under the influence of sunlight, and appears to involve the loss of a chlorine atom from the chloramben molecule. This too, involves a loss of phytotoxicity. It should be noted that loss of phytotoxicity is not a suitable measure of the extent of hydrolysis or photodegradation as these processes may well proceed by way of degradation products which have some level of phytotoxicity.

i. Hydrolysis

Hydrolysis data are required to support the registration of all manufacturing-use products and end-use formulations of chloramben.

Sodium Chloramben

Chloramben free acid and its salts (sodium, ammonium, etc.) appear to be resistant to hydrolysis, judging from data showing the retention of phytotoxicity after several weeks of chloramben in non-sterile moist soils (Sheets, 1963, 05107). More recent data (Union Carbide, 1980, 0172) show that when protected from light, chloramben acid undergoes slow degradation

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in aqueous solution. Eighty-five percent or larger amounts of chloramben initially present were recovered after one year at an acid pH and 25°C.

These studies will partially satisfy Agency requirements for hydrolysis data on sodium chloramben. Data are needed on hydrolysis at other pH's for sodium chloramben.

Methyl Chloramben

The methyl ester is susceptible to hydrolysis by bacterial action in soil which contains enough moisture to support bacterial activity. An Amchem document (Amchem, 1966, 0148) showed that the methyl ester gave no measureable hydrolysis in 48 hours when in contact with well water at a pH of 5 to 6; however, when soil (and therefore bacteria) was present in the water there was a measurable hydrolysis within 48 hours, involving a cleavage of the ester bond to yield the free chloramben acid.

The methyl ester is hydrolyzed in moist soil to the free acid; however, if the soil is first sterilized, no breakdown of the ester occurs (Corbin, 1967, 0586; Talbert, 1970, 05111).

The presumption from these studies is that the methyl ester is relatively unaffected by water in the absence of bacteria; however, these data are inadequate to meet the requirements of the section. Additional testing on methyl chloramben are required.

ii. Photodegradation

Photodegradation studies in water are required to support the registration of all chloramben formulations for non-crop uses. Studies in soil are required to support the registration of all chloramben formulations intended for crop uses.

Several studies have been made of the effects of sunlight on chloramben. All these studies are inadequate in that the products of photolysis were not sufficiently identified or characterized. These studies do provide insight into the photodegradation of chloramben.

Chloramben on the surface of field-capacity soil and irradiated for 48 hours lost 38 percent of its herbicide activity, whereas the loss on dry soil was 30 percent. There was a loss of phytotoxicity to oats in 7.5 hours after exposure to sunlight on the surface of field capacity soil (Fickle, 1974, 0589).

An aqueous solution of the sodium salt became yellow-brown, indicating chemical change, upon exposure to sunlight for periods of up to 14 days. The products were not identified except for chloride ions (Crosby, 1969, 0587; Plimmer, 1969, 05106).

Two days exposure to sunlight was sufficient to produce total loss of phytotoxicity of chloramben aqueous solutions to cucumbers. However, similar solutions kept in the dark showed no change in phytotoxicity after 2 days (Hahn, 1969, 0594).

There are no data on the extent of photodegradation under cloudy conditions. Available data on the photolysis of chloramben are not sufficient to determine the effects of light on chloramben. All data are required on both sodium and methyl chloramben per section 163.62-7.

There are no data to indicate whether the first products of photodegradation retain phytotoxic properties, or whether photodegradation involves an immediate loss of herbicidal properties.

b. Metabolism 163.62-8

Data on metabolism are required to determine the nature of pesticide residues and their availability to rotational crops, and to help in the assessment of potential disposal and reentry hazards. Although preliminarydata presented in the following discussions provide insight into the metabolism of chloramben, the data are inadequate and do not satisfy the guideline requirements. The data gaps exist for both methyl and sodium chloramben.

i. Soil Metabolism

Aerobic metabolism studies are required to support the registration of all formulations. Anaerobic soil metabolism studies are required to support the registration of all formulations intended for field and vegetable crop uses.

Sodium Chloramben

An experiment with pure chloramben showed that phytotoxicity to Italian rye grass (8 ppm in soil) became negligible after 16 weeks in a sandy loam and a silty clay loam. In a clay, however, after 16 weeks only about 60 percent of the control level of rye grass growth was present (Sheets, 1968, 05107). These results are probably due to the different levels of bacterial activity in the soils; however, the Agency cannot rule out the possibility that the different results were due to different leaching rates through the soils. Another study (Amchem, 1967, 0043) showed that after a period of 4-6 weeks a rapid loss of chloramben occurs in soils with a high organic content, probably due to the microbial populations reaching a logarithmic phase in their growth cycle at this point.

A study of the effect of pH on loss of herbicide activity showed a similar rate of loss at pH levels of 4.3, 5.3, 6.5, and 7.5, the soil being unchanged in respects other than pH (Corbin, 1967, 0586).

Only minimal data on the metabolism of sodium chloramben are available. Additional data specified in Section 163.62-8(b,c) are needed to determine metabolism of chloramben in soil.

Methyl Chloramben

Soil bacteria cause hydrolysis of chloramben methyl ester to the free acid at a rate directly dependent on the content of water (Amchem, 1965, 1966, 0148). Chloramben methyl ester is hydrolyzed in wet soil by bacterial action. Approximately 50 percent of the compound is converted to the free acid in from 2 to 8 days. When the soil was partially dried the rate of hydrolysis was less, with about 30 percent being hydrolyzed in 14 days. If, however, the soil is first sterilized, no breakdown of the ester occurs (Corbin, 1967, 0586; Talbert, 1970, 05111).

Data provided are insufficient to differentiate between physico-chemical degradation and microbial degradation. Therefore, all data are required per section 163.62-8.

c. Mobility 163.62-9

Data on mobility are required to determine pesticide residue movement in the environment and to assess the potential for loss of usable land and water resources. Data summarized below provide insight into the mobility of chloramben. These data do not satisfy Agency requirements. Mobility data are needed on both sodium and methyl chloramben.

i. Leaching

Leaching data are required to support registration of end-use formulations intended for terrestrial noncrop and field/vegetable crop uses.

Basic to an understanding of the leaching properties of the various forms of chloramben are their aqueous solubilities and their ability to bind to soils. The salts all dissolve freely in water to the extent of about 250,000 ppm; the free acid, about 700 ppm; and the methyl ester, about 120 ppm (McLane, 196?, 0147; Amchem, 1965, 0115). With such solubilities all forms of chloramben, at the levels used in application to soil, should be completely dissolved by 3-inches of rainfall and readily leach through the soil. Therefore, any failure of the herbicide to leach down with such rain would indicate adsorption on soil particles. Available data on the leaching characteristics of chloramben products provide preliminary indications that a potential groundwater contamination problem could exist as a result of chloramben uses.

Sodium Chloramben

Chloramben free acid and its salts (sodium, ammonium) are leached down typically 8 to 12 inches by a 3-inch rainfall (Amchem, 1965, 0115; Rauser, 1963, 0131; McLane, 196?, 0147). An experiment involving 2 soils (a silty clay loam and a sandy loam) in which water was forced upwards by evaporation from the soil surface showed that chloramben (initially placed 5-6 inches below the surface) moved upwards through both soils at a rate similar to that of other aromatic acid herbicides, and faster than the rates of all other groups of herbicides tested (substituted ureas, triazines, thiocarbamates, and toluidines) (Harris, 1967, 0595). Virtually all the chloramben herbicide activity had moved into the top inch of soil. Clearly some fraction of the chloramben had been left exposed on the soil surface and was subject to photodegradation. It has been noted that the nature of the photodegradation products of chloramben is mostly unknown. (See Topical Discussion on Photolysis). Movement of chloramben upwards probably occurs to some extent during any evaporation period such as that following rainfall.

Methyl Chloramben

The solubility of the methyl ester of chloramben is about 120 ppm (Amchem, 1965, 0115; McLane, 196?, 0147). In contrast to the 8 to 12 inch leaching of sodium chloramben by a 3 inch rainfall, the methyl ester is leached down only about 1.5 inches (Amchem, 1965, 0115; Rauser, 1963, 0131; McLane, 196?, 0147). After hydrolysis of the methyl ester in soil (a matter of a few days), the free acid of chloramben leaches as quickly as the salts of chloramben (Talbert, 1970, 05111).

These data are insufficient to evaluate the potential for sodium and methyl chloramben to leach; all studies specified in 163.62-9 b and d are required.

ii. Adsorption/Desorption

A laboratory study using radioisotopic or nonradioisotopic analytical techniques is required to support the registration of all chloramben formulations intended for terrestrial uses. Data summarized below provide insight into the adsorptive/desorptive properties of chloramben. These data do not satisfy Agency requirements. Data are required on both sodium and methyl chloramben.

There have been some studies of the nature of the adsorption process between chloramben free acid and a calcium montmorillonite clay, which indicate that the adsorbed form has a protonated carboxylic acid group and a protonated amine group (Berkheiser, 1976, 0541). Another study on adsorption to a silt loam showed an increase in adsorption by decreasing the pH of the water-soil mixture (Harter, 1969, 0596).

However, all such studies confirm that although chloramben is adsorbed by soil colloids, the amount adsorbed and the strength of the adsorption forces are far less than for many other herbicides. This helps to account for the uniform adsorption and leaching behavior of chloramben in various soil types.

These studies go only a short way to satisfying the requirements of Section 163.62-9(d). All data specified in the section are needed to determine the adsorption/desorption behavior of chloramben.

d. Field Dissipation 163.62-10

Field dissipation studies using representative formulations under actual use conditions are required to support the registration of all chloramben formulations intended for terrestrial uses. The data summarized below provide insight into the dissipation of chloramben. These data do not satisfy Agency requirements. Data are needed on both sodium and methyl chloramben.

No complete field dissipation study has been found in the chloramben literature. However, it is possible to build a picture of chloramben dissipation as a combination of bacterial breakdown in the upper levels of oil and leaching to lower levels of soil where bacterial action is progressively less (Amchem, 1967, 0043). Probably, chloramben finding its way down to these levels remains intact and will travel with any movement of liquid water, with a corresponding dilution. Some fraction of chloramben will move upwards to the surface of soil (through evaporation),where photodegradation will occur given a sufficiently high intensity of sunlight.

However, no data exists with respect to the formulated products containing sodium and methyl chloramben. Therefore, additional studies as described in 163.62-10 b are needed in crop use areas using representative formulations of methyl and sodium chloramben.

e. Accumulation 163.62-11

Data on accumulation are required to determine accumulation in food webs and to assess the potential adverse effects on nontarget organisms.

i. Rotational Crops

Rotational crop studies are required to support the registration of all chloramben formulations intended for field/vegetable crops. Data summarized below provide insight into the accumulation of chloramben in rotational crops. These data do not satisfy Agency requirements. Data are needed on both sodium and methyl chloramben according to 163.62-11 b.

Registrants have the option of completing these studies or of placing the following phrase on labels of all end-use products containing any salt or ester of chloramben:

"Do not rotate to other crops"

Chloramben is readily taken up by soybean plant roots at a rate proportional to its rate of application on the soil. Soybean roots cause decomposition of the carboxylic acid group, releasing carbon dioxide, at the rate of about 1 microgram chloramben in 8.5 hours per plant (Freed, 1960, 0128). However, movement of chloramben away from the roots and through soybean plants is very slow, with no observed tendency to concentrate in any particular regions (Freed, 1960, 0128). By contrast, in barley, chloramben readily passes into the upper parts of the plant (Freed, 1960, 0128). One study has shown that chloramben added to ground soybean seed is firmly held, and requires a prolonged extraction for recovery (Freed, 1960, 0128). However, it should not be assumed that uptake of chloramben by plant roots is the only, or even the preferred, path of uptake. Green foxtail, for examnple, undergoes no control when chloramben is located in the root zone at a soil concentration of 3 ppm, but is well controlled when chloramben is in the shoot zone at the same concentration (Knacke, 1967, 05100).

It is wise to assume that the plants grown on soil treated with chloramben takeup the herbicide, unless there is evidence to the contrary. Morning glory is resistant to chloramben. In a comparison of it with velvetweed, which is susceptible, it was found that both species take up approximately equal quantities of chloramben, with the raate of uptake being faster in morning glory. However, morning glory quickly detoxifies chloramben to N-glucosyl chloramben, while velvetweed glucosylates chloramben at a far slower rate (Stroller, 1969, 05110).

ii. Fish Accumulation

A laboratory study employing radioisotopic or nonradioisotopic analytical techniques is required to support the registration of all chloramben formulations intended for terrestrial noncrop and field/vegetable crop uses.

A flow-through fish accumulation test, acceptable in meeting registration requirements, was performed on Bluegill Sunfish using chloramben and ^{14}C-chloramben (presumably technical acid) at 1 ppm (Iwan, 1978, 0020). Edible and nonedible tissue maximum bioconcentration factors (BCF's) were 1.14 and 2.19, respectively, early in the exposure phase of the study. BCF's declined gradually during exposure and declined rapidly in the depuration phase. Little potential for significant fish accumulation is indicated by this study. Testing is needed on methyl chloramben.

D. Chloramben End-Use Formulations

Chloramben end-use products contain four varieties of the active ingredient: sodium chloramben, methyl chloramben, ammonium chloramben, and monomethyl ammonium chloramben. Requested fate data on sodium chloramben will satisfy Agency requirements for all products containing sodium, ammonium, and monomethyl ammonium chloramben. Requested data on methyl chloramben will satisfy Agency requirements for all products containing methyl chloramben.

1. All Formulations - Exposure Profile

Chloramben is found in low levels in plants and crops grown on chloramben-treated soils. In some plants it is more or less uniformly distributed throughout the plant, and in others (e.g. soybean plants) it tends to remain in the roots.

Chloramben not taken up by plants will escape microbial attack as it is leached downwards. Because of its apparent stability in aqueous solution it is likely to reach depths at which microbial activity is low or absent. This chloramben is likely to enter ground water or well water or be subject to underground movement into streams. Monitoring studies may be required to define adequately the potential hazard. Chloramben appears to be persistent, and therefore poses a potential contamination problem in ground water.

Because of the lack of data on the environmental fate of chloramben in soils or on its presence in ground water, it is not possible to give a quantitative assessment of human or wildlife exposure to chloramben fromthese sources. However, a potential exists for it to reach ground water or well water, and for its movement from soils into streams.

The non-dietary exposure to humans that may arise from the end-use of a formulated chloramben herbicide is that associated with tank mixing, dilution, loading, and application operations. Although there has been to date no data reported on the non-dietary exposure of humans to chloramben as a consequence of these activities, numerous studies have been performed on exposures resulting from comparable activities with comparable chemical formulations. These studies have been reviewed in order to derive numbers that would be suitable for estimating dermal and inhalation exposure levels resulting from mixing, loading, and application of chloramben.

Available studies indicate that dermal and respiratory exposures are the main pathways by which pesticides are absorbed into the human body during application. Exposure data available for three application activities were reviewed: 1) application of liquid by ground boom, 2) mixing and loading of a liquid for either aerial or ground application, 3) application of a liquid by fixed-wing aircraft. Adequate information on application of a granular substance by ground equipment and homeowner application was not available.

Extrapolation of the existing data on other pesticides to chloramben has been carried out on the basis that exposure is proportional to concentration of active ingredient in the spray, other factors being equal. The worst case dermal exposure calculated in this way for chloramben represents a 23% soluble concentrate chloramben formulation mixed with water and applied to soybean fields at the rate of three pounds active ingredient per acre. A closely similar result is obtained if a 2.7 pound a.i. per acre application of a flowable concentrate is made to soybean fields.

It was assumed that the average applicator would spray chloramben on 100 acres per day and on a total of 160 acres per year. A further assumption was that dermal exposure (to liquid formulations) would result in the absorption into the body of 10% of the active ingredient coming into contact with the skin, and that respiratory uptake would result in 100 percent absorption.

Since these calculations are based on applicator exposure to a given quantity of active ingredient per acre sprayed on a constant number of acres, variations in the time spent spraying will not affect the total exposure, nor the results of the calculations. Variations in the percentage of active ingredient likewise will not affect the calculations, as more dilute solution for spraying would necessitate a greater volume of solution to be sprayed per acre in order to obtain the same rate of application per acre.

2. Soluble and Flowable Concentrate: Exposure Profile

Ground Application

Ground application is the primary means by which soluble and flowable chloramben concentrates are applied to crops as a pre-emergence herbicide. This is usually done by the farmer himself and is typically accomplished with a tractor or truck-mounted boom and tank. There are twenty nozzles on the boom located approximately 18" to 20" above the ground (Lewis, 1980). Applicators typically mix, load, and apply the material themselves; however, in some cases mixer-loaders are employed to perform that function separately. Application will take anywhere from six to twelve hours a day.

Miller, et al. (1980) have developed data indicating that applicators of arsenic acid applied in a similar manner will be exposed to concentrations which, when adjusted for penetration and chloramben a.i. (active ingredient) concentration convert to levels of 4.31 to 0.16 mg/day (dermal: 4.29-0.15 mg/day, respiratory: 0.016-0.007 mg/day). Staiff, et al. (1975) have developed numbers for the same ground application activites of paraquat dichloride which, when adjusted for % chloramben concentration and skin absorption, convert to levels of 2.84 to 0.01 mg/day (dermal: 2.82-0.01 mg/day, respiratory: 0.01-negligible mg/day). These numbers are not applicable to levels of exposure received from mixing and loading.

The results of the comparative analyses arte presented in the following text and in Table 5:3. All numbers are presented in units of milligrams per day penetrated chemical. The numbers are also presented as worst and best cases. The best case reflects the use of adequate protective clothing including long-sleeved shirt, hat, and gloves. The worst case reflects the employment of minimal protective clothing not including long-sleeved shirt, hat, or gloves.

Minimum and maximum respiratory exposures reflect the range of field exposure data. In all cases a cautious attitude by the applicator was assumed and accidental spillage was assumed to be minimal.

TABLE 5.3. RANGE OF ABSORPTION LEVELS FOR FORMULATED CHLORAMBEN

	mg/day					
	DERMAL		RESPIRATORY		TOTAL	
ACTIVITY	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum
1. Ground Application of Soluble and Flowable Concentrate[a]						
- farmer/planter	4.29	0.01	0.016	N[b]	4.31	0.01
2. Mixing-Loading of Soluble and Flowable Concentrate[c]						
- mixer-loader (farmer/planter)	16.63	0.08	0.42	0.002	17.05	0.08
3. Aerial Application of Soluble and Flowable Concentrate[c]						
- pilot	2.62	0.08	0.50	0.005	3.12	0.09
- flagger	4.28	0.17	3.47	0.54	8.75	0.71

(a) Miller (1980), Staiff (1975)
(b) Lower than detection level.
(c) Peoples (1979), Staiff (1975)

NOTE: All values on this table have been adjusted for absorption to the body after exposure and for chloramben concentration (a.i.) during application. This was done to develop justifiable comparisons between available data and chloramben applications.

Mixing and Loading

Liquid chloramben is available to field applicators in 5-gallon and 30-gallon containers (Lewis, 1980, 05116). These containers are mixed with water in loading tanks, mounted either on tractors, trucks, or planes. The method of mixing also varies depending on the degree of applicator sophistication. In some cases, commercial applicators employ enclosed siphon systems which greatly reduce the dermal exposure observed. In other cases, containers are simply punctured and poured directly. For enclosed systems levels of exposure have been observed (Peoples, 1979, 05119) that, when adjusted for chloramben concentration, indicate 17.05-0.59 mg/day (dermal: 16.63-0.44 mg/day, respiratory: 0.42-0.15 mg/day). Miller (1980, 05117) indicates, for the same application, levels of 2.27-0.08 mg/day (dermal: 2.27-0.08 mg/day, respiratory: 0.003-0.002 mg/day). In one instance, when a direct transfer system was used, no gloves were worn and the individual mixer-loader was noted as being careless, levels of 94.54-22.63 mg/day were observed (dermal: 94.44-22.53 mg/day, respiratory: 0.1-0.1 mg/day). Approximately 95 percent of this exposure is normally expected to be to the hands (Wolfe, 1961, 05120).

Aerial Application

A very small percentage of the total chloramben applied is by aircraft (Lewis, 1980, 05116). When this method of application is employed, dermal and respiratory exposure occurs during mixing-loading, flying, and flagging operations. Levels for combined dermal and respiratory exposure are estimated to range from 3.12-0.09 mg/day and 9.75-0.71 mg/day for pilots and flaggers, respectively.

Peoples (1979, 05119) has observed combined levels that, after adjustment for chloramben concentrations, are 3.12-0.50 mg/day for pilots (dermal: 2.62-0.4 mg/day, respiratory: 0.50-0.10 mg/day). For the same operations, Miller (1980, 05117) has observed penetration to pilots at 1.27-0.09 mg/day (dermal: 1.26-0.08 mg/day, respiratory: 0.005 mg/day).

Annual Exposure Levels

Presently there is not a great deal of data available on overall annual non-dietary exposure. However, since this exposure estimate is based on information on the calculated daily non-dietary exposure and the annual application rates of the herbicide chloramben, a range of projections can be developed. The following assumption can be derived from the EPA Chloramben Use Summary Report (Lewis, 1980, 05116).

The Use Summary Report indicates that for application of a liquid formulation, a tractor-mounted applicator can treat approximately 80 acres per ten-hour day while, for the same time period, a skid truck-mounted applicator may be able to treat 140 acres. An average rate of 100 acres treated per ten-hour day was assumed for annual exposure purposes.

Plots of land employed for soybean production in the United States are assumed to range in size from 40 to 400 acres. Based on information from University of Illinois representatives, the average soybean acreage is 160 acres.

Chloramben is applied to soybean crops, in the liquid form, at a rate of 2.0 to 3.0 pounds a.i. (active ingredient) per acre. A rate of 2.5 pounds a.i. was assumed as an average.

In view of these assumptions of a 2.5 pound per acre a.i. application rate and a 4,000,000 pound per year consumption, 1,600,000 acres are treated per year. Assuming 160 acre soybean units, there are approximately 10,000 persons exposed to chloramben per year. These persons will be exposed to estimated doses levels of between 27.3 and 0.016 milligrams of chloramben per year, depending upon methods of application and acreage treated. The estimates of annual chloramben penetration levels for the different methods of application and acreages treated are summarized in Table 5-4.

3. Granular Formulations - Exposure Profile

The potential of granular formulations for forming dusts represents a special human inhalation hazard, particularly during loading operations.However, total exposure from granular applications is assumed to be minimal in relation to liquid formulations since no mixing operations are involved. The granular formulation for domestic use involves a shaker canister and exposure from this application method is also assumed to be low.

TABLE 5-4. ANNUAL CHLORAMBEN EXPOSURE ESTIMATES

Soluble and Flowable Concentrates

ACTIVITY	mg/day[a]		mg/person/yr[b]	
	Worst Case	"Best" Case	Worst Case	"Best" Case
1. Ground Application - farmer/planter	4.31	0.01	6.9	0.016
2. Mixing-Loading -mixer/loader (farmer/planter)	17.05	0.08	27.3	0.13
Total: Farmer/Planter Exposure	21.36	0.09	34.2	0.146
3. Aerial Application				
- pilot	3.12	0.09	5.0	0.14
- flagger	8.75	0.17	14.0	1.14

a) Table 5-3.
b) (mg/day) x (1 day treatment/100 acres possible) x (160 acres/person/yr).

CHAPTER VI

RESIDUE CHEMISTRY

A. Introduction

For any pesticide which has uses that may directly result in residues on food or feed, the Agency sets an allowable residue level, or tolerance, for each commodity on which it may occur. A tolerance level for a particular chemical on a particular commodity is a function of the chemical's toxicity, the percentage of an average daily diet comprised by the commodity, and the amount of residue that can be expected to occur on that commodity at the maximum directed rate of application. The total amount of chemical to which a person may be exposed from all sources should always be less than the toxicological estimate of a safe "Allowable Daily Intake."

The herbicide 3-amino-2,5-dichlorobenzoic acid (chloramben) is used in the control of weeds in growing the following food crops: soybeans, transplanted tomatoes, dry beans, snapbeans, corn, peanuts, cantaloupe, lima beans, cucumbers, transplanted peppers, pumpkin and squash, sunflowers, sweet potatoes, and seedling asparagus. Approximately 96 percent of its use is in soybeans, two to four percent is in corn and beans, and two percent or less is used in tomatoes and other crops. A tolerance level of 0.1 ppm has been established for chloramben in all crops listed above (CFR 180.266). In addition a tolerance level of 0.1 ppm has been established for peanut forage, soybean forage, and corn grain, fodder and forage used for animal feeds.

B. Manufacturing use Chloramben

1. Residue Chemistry Profile

Chloramben movement into plants is a passive diffusion process. Entry usually occurs through the roots, and can also occur through the foliage. Two plant metabolic pathways have been described, a decarboxylation and a conjugation to N-glucosyl chloramben. The former should yield 2,5-dichloroaniline, but if it is formed it does not accumulate to levels at which it is detectable. Thus the fate of chloramben which has undergone decarboxylation is unknown. The conjugation reaction yields a relatively stable non-phytotoxic compound. It appears that a plant's susceptibility to the herbicidal effects of chloramben is related to the extent to which it can carry out either of these detoxifying reactions.

Plants vary also in the ease with which chloramben is moved through them. Soybean roots take up chloramben, but there is little upward movement of chloramben from the roots. Generally, chloramben applied to the surface of soybean leaves and taken up by them tends to move downward towards the stems and roots, with only minor movement toward the seeds. Barley roots also easily take up chloramben, but unlike the case with soybeans, chloramben then moves relatively freely to the upper parts of the plant.

In the interval between chloramben uptake, and harvesting and analysis, plant levels of chloramben drop below 0.1 ppm, the general tolerance limit. There are no data on the pathway of loss of chloramben or N-glucosyl chloramben taken up by these plants.

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Some measurements on the uptake, distribution, and excretion of chloramben in animals have been made. It appears that cows exrete ingested chloramben in the urine and feces, but not in the milk. Dogs also excrete chloramben in the urine and feces. If dogs store any part of the ingested chloramben, it probably is not more than about 0.2 percent of the total ingested.

The analysis of low levels of chloramben appears to present no unusual difficulty. The submitted gas chromatographic method is satisfactory in itself, and is clearly capable of modification and improvement as discussed in the Topical Discussion on analytical methods.

2. Data Requirements and Data Gaps

The proposed guidelines for residue chemistry have not been published. Consequently there are no citations for guidelines corresponding to the types of residue chemistry data required to support individual registrations. In general, however, the Agency must have sufficient data to be assured that the residues of the parent chemical and its metabolites have been identified.

Data Gaps

The following data are required to support the tolerances for chloramben:

1) Information on the storage of agricultural material between sampling and residue analysis. Data on the storage conditions, and on the stability of the residues during storage are required.

3. Topical Discussions

a. Use Patterns and Restrictions

Chloramben is applied principally as a pre-emergent herbicide used alone or in combination with other herbicides for the control of weeds and annual grasses in various food crops and ornamentals. The varous formulations of chloramben are registered for use on dry beans (navy, white, kidney, pinto, and lima) peanuts, soybeans, sunflowers, corn, sweet potatoes, squash, pumpkin, asparagus (seedling), transplanted tomatoes and peppers, lima beans, snap beans, cantaloupes, cucumbers, annual and perennial flowers, shrubs, and trees.

Chloramben is available in soluble, flowable, and emulsifiable concentrates and granular formulations containing from 1.3% to 83.0% chloramben.

Formulations are applied at time of planting or immediately following transplanting; on tomatoes and peppers chloramben may be applied at layby. Liquid formulations are sprayed from truck or tractor sprayers or by aircraft; granular formulations are applied from tractor drawn planter or broadcast applicators. Rates of application presented in Chapter 4 range from 2 to 4 pounds active ingredient per acre for food crops and from 4 to 6 pounds per acre for ornamental uses. Formulations are applied only once per season on agricultural crops and twice per season on ornamentals.

Chloramben formulations contain the following label restrictions. Granular and liquid formulations for use on sunflowers have label warnings prohibiting grazing treated areas and using treated plants for feed or forage. The use on peanuts is restricted to Oklahoma and northern Texas. The use on corn is confined to heavy soils in Illinois, Indiana, Iowa, Kansas, Minnesota, Missouri, Nebraska, and Ohio.

With the exception of ornamentals, the uses of chloramben are for food uses and are expected to result in residues in human food and animal feed.

b. Uptake, Distribution, and Metabolism in Plants

In addition to what may remain of an original application of the chemical, residues may also consist of the chemical's metabolites, as formed by the plant crop to which it was applied. The major and minor pathways of the chemical's absorption, transformation, and distribution can be deduced experimentally from the analysis of radiolabeled applications. Applications by various routes, for example to the roots or leaves, will show differences in absorption rates. The distribution of the chemical and its metabolites can be examined by measuring the radioactivity present in various plant fractions. Isolated metabolites can then be characterized by chromatography, partitioning, or electrophoresis. Metabolic transformations often result in an increase of polarity of the foreign chemical to facilitate elimination. Metabolites characterized as highly polar may have undergone conjugation with naturally occurring amino acids, sugars, or sugar acids. Further chemical analysis can help identify the exact nature of the conjugations. Other possible major transformations can occur by hydrolysis, oxidation/reductions, or the breaking of unstable bonds. The absorption, distribution, and metabolic fate of the chemical determine the potential quantity and identity of pesticide residues in plants used for food or feed.

Chloramben movement into plants is a passive diffusion process and does not require metabolic energy (Stoller, 1969, 0538). Chloramben that enters the plant tissue undergoes a conversion to N-glucosyl chloramben (Swanson, 1966, 0169; Frear, 1978, 0556; Colby, 1965, 0553). Formation of N-glucosyl chloramben is related to the carbohydrate content of the plant. Soybeans depleted of carbohydrate reserves absorb less chloramben and produce less N-glucosyl chloramben than do plants under normal illumination (Swanson, 1969, 0538). N-glucosyl chloramben is not phytotoxic while chloramben is. The "resistant" plants such as soybean or morning glory have an efficient glycosylation system in their tissues. The "susceptible" plants (e.g. velvet leaf) do not have an efficient glycosylation system and chloramben accumulates to exert its phytotoxic effect (Stoller, 1969, 0538).

In addition to the glycosylation reaction, the decarboxylation type of reactions have also been reported. Thus soybean roots when treated with ^{14}C chloramben (with $^{14}COOH$) evolve $^{14}CO_2$ (Amchem, nd, 0127). Carrots planted in chloramben treated soil absorb chloramben. Carrot slices when incubated with ^{14}C chloramben evolve $^{14}CO_2$ (Ashton, 1966, 0548). Attempts to find possible degradation products of chloramben, viz., 2,5-dichloroaniline and 2,5-dichlorophenol in lima beans, peppers, sweet potatoes, peanuts and soybeans (Amchem 1963, 0008; 1965, 0076; 1961, 0079; 1963, 0098; 1963, 0106; 1961, 0159; 1964, 0161; 1963, 0162; 1963, 0163; 1964, 0164) grown on chloramben treated soil were not successful.

Pre-emergent Treatment

The movement of chloramben in the plants shows a unique pattern. Soybeans placed in ^{14}C chloramben solution take up chloramben through their roots. Radioautography of these plants revealed very little upward movement of chloramben (Amchem, 1960, 0127). On the other hand, barley, which is susceptible to chloramben, transports chloramben into the upper parts of the plant easily (Amchem, 1960, 0127). The behavior of the root system may be important, together with glycosylation, in determining whether a particular species is susceptible or resistant to chloramben.

Soybeans grown in soil treated with ^{14}C chloramben accumulate chloramben. Plants that had barely emerged from soil contained 23 ppm and 50 ppm of chloramben for a 3 lbs/A and 6 lbs/A application respectively (Amchem, 1961, 0154).

These levels decreased markedly with time to as low as 3.5 percent of the initial level after 56 days. Chloramben that had entered the plant was stored predominantly as a conjugate. No detectable amount of chloramben was found in mature seeds. Glycosylation cannot be involved in this decrease, as radiolabel would remain. Metabolic decarboxylation does not seemingly proceed fast enough to account for the decrease.

Post Emergent Treatment

Though chloramben is used pricipally as a herbicide in pre-emergent applications, some studies have been made to investigate the effects of foliar or post emergence application, mainly with a view to find out the sites where chloramben would accumulate at maturity. Soybean plants grown under greenhouse conditions were applied with ^{14}C chloramben at a rate of 9 lbs/A on the surface of leaves. The accumulation of ^{14}C was studied in the various parts of the plant at harvest. The seeds contained the least amount of radioactivity (16 cpm) as compared with leaves, stems, and roots (279, 1253, 740 cpm respectively) (Amchem, 1961, 0104; 1961, 0157). The direction of movement was downwards from the leaves to the roots. When chloramben was applied post emergent to soybean plants 104-132 days before harvest at a rate of 3 lbs/A, neither soybean seeds nor hay showed chloramben residues higher than 0.1 ppm (Amchem, 1978, 0101).

c. Metabolism in Animals

The identity of residues in animal products used for food may, as with plants, be largely determined by the metabolic fate of the chemical in the living organism. Livestock or poultry may ingest chemicals through treated feed or forage. Gastrointestinal absorption, biotransformation, and body distribution are usually studied by the feeding of animals with the unlabeled or radiolabeled chemical. The degree to which the parent compound and its plant metabolites are absorbed or excreted can often vary with the forage or fodder crop on which the chemical was administered, and so actual feeding practices are usually approximated. Residues in excreta, blood, milk, eggs, or tissue are then measured and characterized.

The majority of crop residue data on raw agricultural commodities (RAC) indicate that detectable residues would not occur in the feed items. Since detectable residues are not expected to occur in feed items metabolism data are not required.

Studies have been submitted which provide insight into the metabolism of chloramben in animals. In order to find out the fate of chloramben in animals, an experiment was conducted where a cow was given chloramben (at 5 ppm level) in feed (St. John Jr., 1970, 0577). Milk, urine, and feces were analyzed for chloramben content. Eighty-eight and one-half percent of the chloramben was excreted in the urine and 4.6 percent in the feces, and no trace was found in the milk.

Similar experiments in dogs have yielded similar results. Two dogs kept on a diet of 0.5 mg chloramben per kilogram body weight per day, six days per week, for four weeks, showed no detectable levels of chloramben (less than 0.01 ppm) in any of their tissues, including fat (Amchem, 1967, 0085). Chloramben levels in feces and urine were measured on pooled samples for each dog for the last week of the study. These levels were consistent with excretion of the major part of the ingested chloramben. These data indicate that no more than 0.2 percent of total administered chloramben are retained in canine tissues after a 28-day experiment.

The data discussed above, on residues of chloramben in animal tissues, are inadequate in that an inadequate number of animals were studied. There are no data on residues of chloramben in poultry and eggs. The data available on bovine metabolism leaves in doubt the fate of approximately seven percent of the fed chloramben.

d. Analytical Methods

There must be available, before a tolerance may be granted, practicable analytical methods for the detection and measurement of the residue and its metabolites. Every commodity considered for a tolerance must have some applicable method. Such methods are often published and widely used; others may involve adaptions of common analytical procedures. In general, any analytical method suggested for consideration must be characterized in four ways: first, there should be some assurance as to the efficiency of the extraction procedure, so that the analysis is not carried out on partial samples; second, the method should afford a measure of the 'total toxic residue', including toxic degradation, metabolic, or other conversion products; third, the method must be thoroughly validated by analyses of representative samples in comparison to blank values significantly lower than the proposed tolerance and; fourth, the validation should conclude with an estimate of sensitivity, i.e., the least concentration of pesticide which can be detected with a reasonable degree of assurance.

At least one method must be suitable as a regulatory enforcement method, in that it does not require the use of untreated crop samples for blanks, that it is rapid, that it makes use of commonly available equipment and reagents, and that it is sufficiently specific to identify and measure a specific pesticide in the presence of other residues likely to occur on the same commodity.

Method of Analysis of Chloramben

Since chloramben is evidently present in a conjugated form, alkaline hydrolysis is necessary to free all the bound chloramben (Amchem, 1963, 0158). Two methods have been used for chloramben determinations, one a colorimetric method and the other involving gas liquid chromatography. The colorimetric method involves a diazotization and coupling of chloramben to N-(1-naphthyl)ethylene diamine dihydrochloride (Amchem, 1964, 0077; 1964, 0107) or to 1-naphthol (Amchem, 1978, 0057), after which the optical absorbance is measured in a spectrophotometer. The gas chromatographic method involves conversion of chloramben to the methyl ester form, which is quantitated in the gas chromatograph (Amchem, 1978, 0057; 1968, 0085; 196?, 0166; 196?, 0167). Further details of these methods are given:

Colorimetric Method

Fifty gram portions of sample are reduced to a fine paste with methanol in a blender. The mixture is warmed on a steam bath after adding sodium hydroxide to hydrolyse chloramben conjugates. The mixture is filtered and the filtrate made strongly acid, and extracted with ethyl ether. The ethereal layer is in turn extracted into an aqueous alkaline solution, which is then made strongly acid and again extracted into ethyl ether. The ether layer is separated and evaporated to dryness. The residue is refluxed with methanol and sulfuric acid to esterify all chloramben free acid. Water and toluene are added; all ester is dissolved in the toluene layer, which undergoes a conventional Florisil clean-up. The methyl chloramben is eluted in the 15 percent ethyl ether-hexane fraction. After evaporation of all the solvent the ester is diazotized (sodium nitrite-acid, then ammonium sulfonate solution) and coupled with N-(1-naphthyl)-ethylene diamine dihydrochloride. The color intensity is measured at the absorption maximum (approximately 528 nm).

The method is sensitive to 0.1 ppm (three times background signal) and gives recoveries of 70-100 percent. It has been validated for pepper, dry beans, pumpkins, squash, sweet potatoes, corn, and peanuts.

This method is not suitable for enforcement purposes because it necessitates the use of a "blank", i.e. carrying a sample through the analytical procedure for comparison with the crop sample of interest.

Gas Chromatographic Method

Twenty-five gram portions of sample are finely ground in a blender and refluxed with methanolic sodium hydroxide to hydrolyse conjugated chloramben. The mixture is filtered (after centrifugation if necessary), water is added, and the solution is evaporated. Addition of water and evaporation is repeated until all methanol is eliminated. The pH is brought to 1.0 and the solution is extracted with diethyl ether. The ether is in turn extracted by an aqueous phosphate buffer (pH 5.8). The aqueous layer is acidified to pH 1 and again the ether extraction is carried out. Chloramben in the ether layer is esterified with diazomethane to the methyl ester, and the solution of methyl chloramben is concentrated to exact low volume (0.5 ml or 1.0 ml). This solution is used for injection into a gas chromatograph, fitted with a 6 foot 3 percent Carbowax 20M column at 230°. The recommended detector is a microcoulometric detector used in the halogen mode. Alternatively, an electron capture detector may be used. Retention time is about 15 to 20 minutes (50 ml nitrogen carrier gas per minute). If a 5 ft. x 1/8 in. 5 percent QF-1 column at 200° isothermal is used, the retention time of the methyl ester is about 5 minutes.

The lower sensitivity (three times background) of this method is about 10 nanograms of methyl ester, which corresponds to 10 ppb chloramben in the original sample. The method has been validated for lima beans, soybeans and soybean forage, peanuts, corn and corn silage, and navy beans.

This method is suitable for enforcement purposes, as it has adequate sensitivity, precision, and specificity, and does not require the use of a "method blank". It is capable of further improvement, however, notably in speed and efficiency of extraction of residues from plant materials.

e. Residue Data

In addition to provisions for analytical methodology, a second prerequisite to the granting of tolerances is the generation of supporting data. Residue experiments generally consist of:

1) Data about the stability of extracted residues under storage;
2) An examination of raw consumable commodities for residues of the pesticide chemical after treatment corresponding to the proposed uses.

Residue data generally disclose: the nature of the residue (i.e., parent compound or transformation product); the level of the residue as it occurs in the whole raw agricultural commodity, the commodity being in the form in which it moves in interstate commerce; the distribution of the residue in the processing of the commodity for consumption, including washing, brushing, trimming, curing, drying, cooking, or canning. Some data may be available comparing various methods for the intentional removal of residues. Residue data can be obtained by field experiments, by animal treatment studies, by soil persistence studies, or by the monitoring of actual residues in marketed food or feed products, by which tolerances can be enforced or reassessed.

Soybeans

The recommended application rate for soybeans is 2-3 lbs/acre. Soybean plants of Harosoy variety treated with chloramben at 4 and 8 lbs/acre pre-emergent, did not show more than 0.1 ppm of chloramben residues in the mature beans (Amchem, 1965, 0071).

Soybeans of Clark 63 variety treated with cloramben pre-emergent at the rate of 6 lbs/A and harvested after an interval of 110 days showed a residue content of less than 0.04 ppm in the mature beans. (Amchem, 1968, 0084)

When chloramben was applied (1.5-2.0 lbs/A) as a mixture with vernam TE (2 lbs/A) pre-emergent, the residue levels in soybeans from three locations representing two varieties (Woodworth, Williams) were less than 0.02 ppm whether bean or forage was analyzed. (Amchem, 1979, 0041)

Soybeans of the "Hill" variety were treated with a liquid formulation of chloramben at a rate of 4 or 8 lbs per acre. Analysis of soybeans at maturity showed a residue content of less than 0.1 ppm for both rates of application. (Amchem, 1967, 0044)

Five varieties of mature soybeans (Clements, Amsoy, Wayne, Beeson, Williams) from five field experiments were analyzed for residues of trifluralin and chloramben, by gas field chromatography. In these tests, trifluralin and chloramben were applied as a pre-emergent tank mix combination at 1-2 and 2.5-5.0 lbs/A, respectively. Residues of chloramben ranging from 0.02-0.06 ppm were measured in three samples while no detectable residues were found in the two remaining samples. (Amchem, 1978, 0050)

Samples of soybeans and soybean plants from either locations representing six varieties (Amsoy, Adelphia, Corsoy, Lee, Dare, Hill) were treated with a formulated mixture of sodium salt of chloramben plus Lorax (N-3,4-dichlorophenyl-N-1-methoxy-N-1 methyl urea). Plants were treated at a rate of 1 1/2 lbs. of chloramben plus 1/2 lb. of Lorax per acre and also at twice this rate. Chloramben content was determined by gas liquid chromatography. No residues of chloramben greater than 0.1 ppm were found in soybeans or soybean forage. The samples taken at a very early harvest (38 days after treatment) as well as samples treated at twice the normal rate also showed no chloramben residues greater than 0.1 ppm. (Amchem, 1978, 0057)

Soybean and soybean hay samples from six locations were analyzed for chloramben residues resulting from post emergence treatment with chloramben (3 lbs/A, 104 to 132 days prior to harvest). None of the treated or control samples showed residues of chloramben greater than 0.1 ppm when analyzed by a gas-liquid chromatographic method. The recovery of chloramben from fortified samples ranged from 70 percent to 108 percent with an average of 87 percent. (Amchem, 1978, 0101)

In a greenhouse study soybean seedlings were treated with chloramben ^{14}C (^{14}C in the carboxyl group) on the leaf surface at a rate of 9 lbs/A. The plants were allowed to grow to maturity. The leaves were collected upon abscission.

At harvest roots, stems, pods, and seeds were analyzed for ^{14}C content. The seeds showed the least amount of radioactivity, while the stems and roots contained the bulk of radioactivity. (Amchem, 1961, 0104)

Nine sets of samples from nine locations representing eight varieties of soybeans (Lee 68, Adelphia, XK505, Wells, Williams, Amsoy 71, Amsoy, Chippewa 64) treated with 3 lbs. of active ingredient of chloramben per acre, were analyzed for chloramben and trifluralin residues. None of the samples showed any residue of chloramben greater than 0.1 ppm nor any residue of trifluralin greater than 0.05 ppm. (Amchem, 1975, 0109A)

In another study, four sets of samples from four locations representing four varieties of soybeans treated with 1 1/2 to 3 lbs. of active ingredient of chloramben per acre in combination with another herbicide failed to show chloramben residue greater than 0.1 ppm. (Amchem, 1975, 0109A)

Neither of two sets of samples (XK505 and Harosoy) from two locations, treated with 1.5 lbs. plus 1.5 lbs. active ingredient of chloramben per acre, nor a sample (Amsoy 71) treated with 3 lbs. of active ingredient of chloramben showed a residue content higher than 0.1 ppm on analysis. (Amchem, 1975, 0109A)

Three varieties of soybeans (Hill, Clark 63, and Amsoy) at five locations were treated with both liquid and granular formulations containing mixed amine salt of chloramben, at a rate of 3 and 6 lbs. per acre. Mature beans, immature beans and pods, immature plant or whole plant were all analyzed for chloramben content and no residue greater than 0.1 ppm was detected. (Amchem, 1967, 0120)

Ten varieties of soybeans (Clay, Corsoy, Clark 63, Swift, Harosoy 63, Wayne, Amsoy 71, Teweles 304, Woodworth, Williams) in 14 locations were treated with chloramben as a tank mix with alochlor at rates ranging from 2-3.3 lbs. of chloramben per acre. None of the treated samples showed residues of chloramben equal to or greater than 0.1 ppm. (Amchem, 1976, 0118)

The chloramben content of de-oiled soybean cake and soybean oil from mature soybeans representing four varieties (Harosoy, Lindarin, Hill, and Lee) treated with chloramben at 8-9 lbs. per acre were analyzed. Except for one instance of Lindarin soybean cake showing a chloramben content of less than 0.2 ppm, no residue was found in other samples. (Amchem, 1961, 0135)

Soybean plants treated pre-emergent with ^{14}C labeled chloramben at 3 and 6 lbs. per acre and grown under greenhouse conditions showed very little chloramben in the bean pods as compared with the other parts of the plant which contained the bulk of chloramben. At a chloramben application rate of 3 lbs. per acre, 0.1 ppm was present in bean pods. The upper, middle, and lower thirds of the plant contained 0.47, 0.89, and 1.39 ppm, respectively. When the application rate was 6 lbs. per acre, the bean pods showed a residue content of 0.2 ppm. The upper, middle, and lower thirds of the plants showed a residue content of 0.87, 2.72, and 5.32 ppm, respectively. (Amchem, 1961, 0136)

In general, residues of chloramben in soybeans are below tolerance levels.

Peanuts

Peanuts of the "Starr" variety from five locations were treated with a liquid formulation of chloramben at a rate of 6 lbs/acre (twice the recommended rate) 18, 72, 95, 141, and 179 days before harvest, and the residue content of peanuts was analyzed. All the samples that had received treatment 72 to 179 days before harvest showed residues less than 0.1 ppm. The samples that were harvested 18 days after treatment with chloramben showed a residue content of 0.43 ppm. (Amchem, 1967, 0044)

Peanut plants treated with chloramben at 6 lbs/acre (twice the recommended rate) were harvested and the presence of 2,5-dichloraniline, a possible metabolite of chloramben arising through a decarboxylation reaction, was measured in the peanut hulls and meat. The method used was sensitive to 0.1 ppm and no traces of 2,5-dichloraniline was found in the hulls or the meat portion of peanuts. (Amchem, 1965, 0076)

Analysis of peanut hulls, foliage, and nuts collected 95-151 days after treatment did not show any residue of chloramben. Foliage collected 72 days after treatment had less than 0.1 ppm residue. Foliage collected 18 days after treatment showed 0.42 ppm. (Amchem, 1965 estimated, 0077)

Peanuts of the "Starr" variety when treated at the rate of 6 lbs/acre with chloramben 101 days before harvest showed a residue content of less than 0.4 ppm. (Amchem, 1968, 0084)

Peanuts of "Spanhorima", "Starr", and "Spancross" varieties in three locations were treated with chloramben at the rate of 3 lbs/acre 138, 112, and 162 days before harvest. The residue content of the harvested peanust was less than 0.1 ppm. (Amchem, 1975, 0109A)

These data indicate that peanuts treated with recommended levels of chloramben are not likely to contain residues above tolerance levels.

Peppers

The recommended rate of application is 4 lbs/acre. Peppers of four varieties (Yellow Wonder, World Beater, California Wonder, Delaware Bell) in three locations were treated at 4-16 lbs/acre 50 to 81 days before harvest. In all cases the harvest peppers contained less than 0.1 ppm of chloramben residue. (Amchem, 1967, 0044)

Chloramben treated peppers showed less than 0.1 ppm of 2,5-dichloroaniline, a potential metabolite of chloramben arising from decarboxylation. (Bois, 1964, 0093)

Peppers of five varieties (California Wonder, Bell, Cannoe, Keysonte Resistant Giant, Yellow Wonder) on eight locations were treated with chloramben at the rate of 4 lbs/acre 36, 47, 51, 52, 59, 60, 68, and 77 days before harvest. All the peppers analyzed showed residues less than 0.1 ppm. (Amchem, 1975, 0109A)

Yellow Wonder peppers and World Beater peppers were treated with 11 and 16 lbs/acre respectively and no traces of 2,5-dichloroaniline was found using a method sensitive to 0.1 ppm. (Amchem, 1963, 0162) In another study Yellow Wonder and World Beater peppers were treated with chloramben at rates of 8 and 16 lbs/acre and were harvested in two batches one after 50 days of treatment and the other after 70 days of treatment. Analysis of the peppers showed less than 0.1 ppm chloramben residues in all the cases irrespective of dosage or the interval elapsed before harvest. (Amchem, 1964, 0008)

These data indicate that chloramben residues in peppers will not be above the tolerance level when treated at the recommended rate.

Tomatoes

The recommended application rate is 4 lb/acre. Five varieties of tomatoes were treated with chloramben at rates ranging from 6 to 16 lbs/acre. The residue content of immature green, mature green, and mature red tomatoes was not greater than 0.1 ppm in all cases (Amchem, 1967, 0044).

Chloramben residues ranged from 0.03 to 0.05 ppm in tomatoes treated at a rate of 4 lbs/acre. When the application rate was 8 lbs/acre the residue levels ranged from 0.05 to 0.14 ppm. (Amchem, 1963, 0106)

Tomatoes of "Heinz 1439", "Campbell 28", "Marglobe", and "Heinz 1327" showed chloramben residue content of less than 0.1 ppm in the mature fruit, when the plants had been treated at 4 lbs/acre. The time elapsed from treatment to harvest ranged from 25 to 112 days in these studies. (Amchem, 1975, 0109A)

In a laboratory radiotracer study, pure chloramben labeled in the carboxyl group with ^{14}C was used on tomatoes grown under greenhouse conditions. Chloramben was used at rates equivalent to 3 or 6 lbs/acre, 63 days before harvest. At an application rate of 3 lbs/acre the fruits contained residues of 0.06 ppm but at 6 lbs/acre the residues were 0.15 ppm. Plants that have received treatment at layby (22 days before harvest) of 6 lbs/acre showed a residue content of 0.52 ppm in the fruits (Amchem, 1963, 0102). Treatment of tomatoes under actual field conditions will not, in all probability, occur at less than 60 days before harvest.

In general, the data indicate that residue levels in tomatoes will not exceed tolerances.

Lima Beans

The recommended rate of application is 2-4 lbs/acre. Lima beans from five locations that had been treated with chloramben at the rate of 6 lbs/acre ranging from 73-98 days before harvest, showed less than 0.1 ppm of chloramben residues. (Amchem, 1967, 0044)

Lima beans from two locations where chloramben was applied at twice the recommended rate showed no residue of 2,5-dichloroaniline, a potential metabolite that arises from decarboxylation of chloramben. (Amchem, 1963, 0098)

In a radiotracer study lima beans grown in a greenhouse were treated with ^{14}C- labeled chloramben at the rate of 3 and 6 lbs/acre. Analysis of the mature bean showed a residue content of 0.03 ppm when the recommended rate of 3 lbs/acre was employed. At the exaggerated level of 6 lbs/acre the residue content was 0.09 ppm. The immature beans showed a residue content of 0.08 ppm at 3 lbs/acre rate and 0.22 ppm at 6 lbs/acre rate of application. (Amchem, 1963, 0108)

Lima beans from four locations representing four varieties (Mibres, Bridgeton, Thergreen, Fordhook Bush) treated at rates of 3-4 lbs/acre, 70-94 days before harvest failed to show chloramben residues greater than 0.1 ppm. (Amchem, 1975, 0109A)

In summary, recommended application rates of chloramben on lima beans result in residues below the tolerance limit.

Corn

The recommended rate of application is 2 lbs/acre. Corn plants were treated at 3 lbs/acre and 9 lbs/acre. The corn at tassel stage and immature ears were harvested after 41, 66, and 101 days, respectively after chloramben treatment and on analysis showed less than 0.1 ppm of chloramben residues. (Amchem, 1967, 0044) At a dosage of 4 lbs/acre and 16 lbs/acre treatment, the silage, mature corn kernels and mature corn cob (84, 119, 119 days after treatment, respectively) showed no greater than 0.1 ppm of chloramben. (Amchem, 1967, 0044) Corn treated at 2 and 6 lbs/acre and harvested after 139 or 190 days showed a residue content less than 0.1 ppm. (Amchem, 1967, 0044)

No residues were found in silage, corn kernels, or corn cobs harvested from different locations that had been treated as high as 16 lbs/acre (eight times the recommended rate). (Amchem, 1965 estimated, 0080) Analysis for the potential metabolite 2,5-dichloraniline was conducted on silage and kernels collected from the 16 lbs/acre treatments and no traces of this material were found. (Amchem, 1965 estimated, 0080)

Corns of different varieties treated with chloramben at 1.5 to 2 lbs/acre or in combination with atrazine, did not show residues greater than 0.1 pm in corn (samples consist of silage, immature ears, immature whole plant and whole plant). (Amchem, 1975, 0109A) Corn samples from four different locations representing four varieties of corn (PAG 5X7, Pioneer 3206 and Agway 800, McCurdy 95) that had been treated with a formulation of chloramben plus atrazine 1+2 lb/A or 2+4 lb/A were analyzed and no residue of chloramben greater than 0.1 ppm was found. The atrazine levels were less than 0.25 ppm in the same samples. (Hazleton Labs, 1969, 0110)

These data indicate that residues below tolerances are found in corn treated in accordance with label recommendations.

Sweet Potatoes

The recommended rate of application is 4 lbs/acre. Sweet potatoes of "Georgia Red" and "Tenhoma" varieties treated with a liquid formulation of chloramben at the rate of 4 or 8 lbs/acre 145-197 days before harvest did not show chloramben residue content greater than 0.1 ppm (Amchem, 1967, 0044).

Use of either liquid or granular formulations of chloramben at the rate of 6 lbs/acre 111 days before harvest did not show a chloramben residue more than 0.1 ppm. Sweet potatoes of "Nemagold" variety were treated with granular or liquid formulation of chloramben at rates of 8 lbs/acre (or 9 lbs/acre in one case) did not show residues greater than 0.1 ppm (Amchem, 1967, 0044).

Sweet potatoes of "Centennial" variety when treated with a liquid formulation of chloramben at 6 or 32 lbs/acre 117 days before harvest showed no residues of chloramben greater than 0.1 ppm (Amchem, 1967, 0044).

In a rate of disappearance study sweet potatoes of the "Nemagold" and "Yellow Sweet Potato" variety were treated with a liquid formulation of chloramben at 16 lbs/acre. Analysis of yellow sweet potatoes harvested at three stages very immature (56 days after treatment), immature (97 days after treatment), and mature potatoes (124 days after treatment) showed residues contents of 2.5 ppm, 0.25 ppm, and less than 0.1 ppm, respectively. Analysis of the "Nemagold" variety at very immature (61 days), immature (79 days) and mature (111 days) stages showed a residue content of 0.11 ppm, less than 0.1 ppm, and less than 0.1 ppm, respectively (Amchem, 1967, 0044).

Sweet potatoes treated at the exaggerated levels of 32 lbs/acre did not show any residue of 2,5-dichloroaniline, a potential metabolite of chloramben (Amchem, 1965 estimated, 0078).

Two varieties of sweet potatoes ("Centennial" and "Yellow") from four locations treated at 4 lbs/acre 116-125 days before harvest did not show more than 0.1 ppm of chloramben residues (Amchem, 1975, 0109A).

Residues of less than the tolerance level occur in sweet potatoes treated at the recommended application rate.

Pumpkin, Squash

The recommended rate is 2-4 lbs/acre. In a rate of disappearance study squash of "Crookneck" variety were treated at 8-12 lbs/acre and the squash vines, immature fruit, mature fruit (early harvest), and mature fruit (late harvest) were analyzed for chloramben residue content. All the samples showed less than 0.1 ppm residue (Amchem, 1967, 0044).

Seven squash varieties (Table Queen, Buttercup, Butter Nut, Yellowneck, Green Hubbard, Boston Marrow, Zucchini) from seven locations were treated at the rate of 8 lbs/acre with a granular formulation of chloramben and harvested after 100-144 days of treatment. In all the cases the chloramben residue content was less than 0.1 ppm (Amchem, 1967, 0044).

Pumpkins of the type "Big Tom" and "Small Sugar", treated at the rate of 8 lbs/acre 100-104 days before harvest did not show any chloramben residue greater than 0.1 ppm. "Kentucky Field" pumpkins when treated with a granular formulation of chloramben at the rate of 3 lbs/acre 119 days before harvest showed residues less than 0.1 ppm (Amchem, 1967, 0044).

Pumpkins of the Jack-o-Lantern variety showed less than 0.04 ppm of chloramben residues when treated with chloramben at 6 lbs/acre 111 days before harvest (Amchem, 1968, 0084).

Squash of four varieties, (Butternut, Golden Summer Crookneck, Yellow Crookneck, Golden Hubbard) from six locations treated with chloramben at a rate of 2 to 4 lbs/acre 53-90 days before harvest failed to show chloramben residues greater than 0.05 ppm (Amchem, nd, 0109).

Using a method sensitive to 0.1 ppm, no trace of 2,5-dichloroaniline, free or bound was found in Big Tom pumpkin, Acorn squash, and Zucchini treated at twice the recommended rate of chloramben (Amchem, 1964, 0164).

These data show chloramben applied at the recommended rate gives residues below the tolerance limit for pumpkin and squash.

Dry Beans and Snap Beans

The recommended rate of application is 2-3 lbs/acre. Beans of five varieties (Red Kidney, Pinto, Pinto U.I. III, Navy Beans, great Northern) treated with a liquid formulation of chloramben at rates of 3-8 lbs/acre showed no chloramben residues higher than 0.1 ppm (Amchem, 1967, 0044).

Navy beans of the "Gratiot" variety treated with chloramben at the rate of 3 lbs/acre showed a chloramben residue content of less than 0.04 ppm (Amchem, 1968, 0084).

Chloramben treated dry beans showed less than 0.1 ppm of 2,5-dichloroaniline, a potential metabolite of chloramben (Amchem, 1964, 0093).

"Great Northern" dry beans treated with chloramben at the rate of 4 lbs/acre and "Pinto" dry beans treated at the rate of 8 lbs/acre failed to show 2,5-dichloraniline higher than 0.1 ppm using a method sensitive to 0.1 ppm (Amchem, 1963, 0008).

Beans of different types treated with chloramben at different rates ("Great "Northern" 3-4 lbs/acre, "Red Kidney" 3 lbs/acre, "Navy" 2 lbs/acre, "Pinto" 3-8 lbs/acre) did not show a residue of chloramben higher than 0.1 ppm (Amchem, 1964, 0096).

Four varieties of snap beans (Tender Pot, Black Valentine Bush, Blue Lake, Tender Crop Gal Val 50) from four locations treated with chloramben at the rate of 4-8 lbs/acre 52-98 days before harvest, showed chloramben residues less than 0.1 ppm (Amchem, 1968, 0149).

These data show that residues below tolerances result from use of chloramben on "dry" beans and snap beans.

Cucumber

The recommended rate of application is 2-3 lbs/A. Three varieties of cucumbers (Crispy Formula 58, Burpee Pickler, Sunnybrook Slicer) treated with chloramben at the rate of 2 to 8 lbs/acre 69-71 days before harvest did not show chloramben residues greater than 0.1 ppm in the fruit (Amchem, 1968, 0149).

Melons

The recommended rate of application is 2-3 lbs/A. Musk melon ("Samson Hybrid"), watermelon ("Sugar Baby") and cantaloupe (Hale's Best Jumbo) treated at 8, 6 and 6 lbs/acre, respectively, showed no detectable chloramben residues in the fruit (Amchem, 1968, 0149).

Sunflower

The recommended rate of application is 2-3 lbs. per acre.

Sunflower plants (Peredovik, Sun Hybrid 304, and an unknown variety) were treated with a Chloramben/trifluralin tank mix (3 lbs/acre chloramben plus

1 lb/acre trifluralin) 122 to 135 days before harvest. The whole seeds on analysis contained less than 0.01 ppm of chloramben and less than 0.05 ppm of trifluralin (Amchem, 1979, 0100).

Adequacy of Residue Data

Several crops which may be treated with chloramben are further processed after harvesting, in the course of which may occur a concentration of any residues of chloramben. These comprise tomatoes (to tomatoe pastes and purees), soybean (to soybean oil), peanuts (to peanut oil), sunflowers (to sunflower oil), and corn (to corn oil).

Available crop residue data on tomatoes, soybeans, peanuts, and sunflowers indicate that, in general, residues do not occur at detectable levels on the raw agricultural commodities at harvest. Therefore, processing studies are not required.

Residues in Meat, Milk, Poultry, and Eggs

For this Section, data should show whether residues will result in meat (muscle, liver, kidney, fat), poultry, eggs, or milk. The toxicant fed should correspond to the aged residues found in the item of feed, which may or may not be the parent pesticide. The studies should be performed at several dosage levels, including exaggerated dosages, preferably threefold and tenfold.

The bulk of residue data on raw agricultural commodities (RAC) indicate residues below tolerance levels. Since data indicate that residues are present below the level of detection, feeding studies are not required.

4. Dietary Exposure

The exposure of humans to pesticide residues from registered use via the food chain is a function of several factors:

a) The established tolerance for a commodity (in ppm)
b) The percentage of a commodity in the daily diet.
c) The percent of that commodity that is treated with the pesticide (an adjustment factor for total population exposure).
d) The assumed amount of food consumption by an average person, 1.5 kg per day.
e) The assumed body weight of an average person, which is 60 kg.

When these factors are substituted into a formula (i.e, (a x b x c x d) divided by e), the human exposure to those pesticide residues in a commodity is found in terms of mg of pesticide per kg of body weight per day.

This potential daily exposure is compared with an 'Allowable Daily Intake', which is set on the basis of toxicological 'No Observable Effect Level', plus a margin of safety factor of 100x, to allow for a 10x greater sensitivity of humans over test animals, and to allow for the possibility of an individual who is 10x more sensitive than the average person. In order to determine the 'No Observable Effect Level' for a pesticide chemical, the Agency must have adequate acute and chronic studies.

The estimates of human dietary exposure to chloramben are presented in Table 5-1 and are based on tolerance levels. The data indiate that dietary exposures to chloramben will range from less than .0005 to 0.013 mg/day (0.000008 to 0.00022 mg/kg body weight). Annual dietary exposure is then estimated at from less than 0.16 to 4.7 mg/person. The maximum value reflects the possibility that a person's diet includes all chloramben-treated crops, when in actuality this is unlikely to occur. Chloramben is used on only seven percent of soybean crops, four percent of tomato crops, thirteen percent of bean crops, three percent of peanut crops and less that one percent of corn crops in the United States. The minimum values (or adjusted values) in Table 5-1 reflect adjustments for these particular crops.

C. Chloramben End-Use Formulations

1. Registration Requirements

There are no residue chemistry data required for the non-food use of chloramben.

For future registration of a product for use on a food or feed crop not covered by this Standard, the Agency must be provided with a petition for tolerance, a full range of data including a validated method for analysis of residues in or on the raw agricultural commodity, data on metabolism of chloramben in plants and (when appropriate) in animals, and residue data reflecting the proposed use of the pesticide on the crop.

TABLE 6-1
DIETARY EXPOSURE TO CHLORAMBEN

	Tolerance ppm	Food Factor	Daily Intake mg/day mg/day	Adjusted Dietary Intake[a]
Soybeans	0.1	0.92	0.0014	0.0001
Tomatoes	0.1	2.87	0.0043	0.00015
Lima Beans	0.1	0.19	0.0003	0.00004
Corn	0.1	1.00	0.0015	0.00002
Peanuts	0.1	0.36	0.0005	0.00002
Beans, Dry, Edible	0.1	0.31	0.0005	0.00006
Cantaloupe	0.1	0.52	0.0008	0.00001
Cucumbers	0.1	0.73	0.0011	0.00001
Peppers	0.1	0.12	0.0002	0.000002
Pumpkin	0.1	0.11	0.0002	0.000002
Beans, Snap	0.1	0.98	0.0015	0.000002 .
Squash	0.1	0.11	0.0002	0.000002
Sunflower	0.1	0.03	0.0001	0.00001
Sweet Potatoes	0.1	0.40	0.0006	0.00001
TOTAL			0.013	0.00045

a) When data available, values based on percentage of sites treated with chloramben. For site where percentage of treatment is unknown, one percent is assumed.

CHAPTER VII

TOXICOLOGY OF CHLORAMBEN PRODUCTS

A. Introduction

A wide range of chloramben products are currently registered for use. Manufacturing-use products consist of sodium chloramben and methyl chloramben. End-use formulations contain chloramben as the active ingredient, present as the sodium salt, ammonium salt, monomethyl ammonium salt or methyl ester.

Toxicology testing is required for registration of all manufacturing-use products and end-use formulations of chloramben. The majority of tests (acute and chronic) are to be performed on the manufacturing-use product or the technical grade of the active ingredient, if different. Acute toxicity testing of all end-use formulations must also be conducted. For purposes of extrapolating toxicology safety data, the sodium salt of chloramben has been determined to be equivalent to chloramben (3-amino-2,5-dichlorobenzoic acid). A summary report in Agency files indicates that the methyl ester of chloramben hydrolyzes to chloramben acid, through microbial degradation, within days of application to soil. Provided evidence is submitted documenting this reaction, all data requirements associated with the food-use pattern of methyl chloramben may be fulfilled through testing with chloramben acid or the sodium salt.

A potential RPAR (Rebuttable Presumption Against Registration) trigger study on technical chloramben conducted by the National Cancer Institute (NCI) indicated that chloramben administration resulted in hepatocellular carcinoma in female mice. Three additional chronic feeding studies, employing a lower dose range than the NCI study do not indicate oncogenic potential. However, these studies are of limited value for measuring the oncogenic potential of chloramben since the MTD (Maximum Tolerated Dose) was not used. Available mutagenicity testing is negative.

Toxicological data submitted to date are primarily on technical chloramben. Some data have been submitted on sodium and methyl chloramben and end-use formulations containing either methyl chloramben, ammonium chloramben, sodium chloramben or an ammonium chloramben/monomethyl ammonium chloramben mixture.

B. Chloramben Manufacturing-Use Products

1. Toxicology Profile

a. Sodium Chloramben

The Agency has determined that data requirements for sodium chloramben may be fulfilled by testing with technical chloramben (3-amino 2,5-dichloro benzoic acid). The high acute oral LD_{50} of 100% technical chloramben (5,620 mg/kg) in male rats suggests a very low acute oral hazard to human beings. Gross pathologic changes included congested lungs, kidneys, and adrenals. Dermal LD_{50} values of 3,160 mg/kg and greater than 5 g/kg, respectively, for technical chloramben (100 percent purity) and sodium chloramben (85 percent chloramben acid equivalent) administered to male and female albino rabbits indicate a low potential for human dermal toxicity. Based on the LC_{50} determination of greater than 200 mg/l (sodium chloramben) in male and female rats, a low acute inhalation hazard is expected. Sodium chloramben may irritate human eyes based on a primary eye irritation study in albino rabbits. Mild to moderate conjunctival irritation persisting for 7 days was noted in this study.

No subchronic dermal or feeding studies are available on either technical chloramben or sodium chloramben. Two-year feeding of technical chloramben (97 percent purity) to male and female beagles did not result in any toxic effects. Slight to slight-to-moderate vacuolation of liver cells was noted in 3 of 8 dogs at the high dose level (10,000 ppm). The "No-Observed Effect Level" (NOEL) for the study is 1,000 ppm (25 mg/kg body weight/day).

A 1963 chronic feeding study in albino rats will not satisfy Agency requirements because of insufficient test animals, a high incidence of non-chloramben related mortality, disparity of animal weights, and limited histopathological reporting. A 1979 chronic feeding study in rats reported that chloramben in the diet at concentrations of 100, 1,000, and 10,000 ppm did not cause any significant effect.

An oncogenic study on technical chloramben (90-95 percent purity) by the National Cancer Institute concluded that chloramben was carcinogenic to female mice, producing hepatocellular carcinoma. The Agency considers the NCI Bioassay, although flawed, adequate for risk assessment. An eighteen month oncogenic study of technical chloramben conducted by Huntingdon Research Center concluded that chronic ingestion of the compound by CD-1 mice did not result in any compound-related tumors at dosages less than the maximum tolerated dose (MTD). Primary compound associated tissue alterations were confined to the liver in all treated mice and were compatible with that observed in enzyme induction. No dose-related trends in benign or malignant tumors were identified in the 1979 chronic feeding study in rats discussed above. However, the dosages employed in this study (100, 1,000, and 10,000 ppm) were also less than the MTD.

A sub-mammalian point mutation test (no metabolic activation) using technical chloramben (90-99 percent purity) was not mutagenic to the test organisms. Further mutagenicity testing is required as are teratogenicity studies.

A very limited metabolic study indicated no retention of the compound in the liver, kidney, muscle, fat, and blood of dogs fed chloramben. Residues in the urine and feces were detected.

b. Methyl Chloramben

Although the acute toxicity properties of the methyl ester of chloramben are expected to differ from those of the sodium salt, the effects of chronic exposure as a result of food ingestion are similar based on the breakdown of the methyl ester in soil to chloramben acid.

The methyl ester of chloramben has a higher acute toxicity than does either technical chloramben or sodium chloramben. The acute oral LD_{50} value of 1,710 mg/kg following administration of the technical methyl ester to male rats results in a Toxicity Category III designation, still indicating a generally low acute oral toxicity hazard. Major necropsy findings include congestion of the lungs, liver, kidney, and pancreas; pale-appearing spleen; and gastrointestinal inflammation.

No other testing was conducted with the technical methyl ester of chloramben.

2. Human Risk Assessment Evaluation

a. Acute Exposure

The chloramben exposure profile (see Environmental Fate Chapter) reveals that persons who handle, store or ship the manufacturing-use products sodium chloramben and methyl chloramben will be exposed principally by the dermal route. Without proper precautions, the compound may get in the eyes.

Based on the previous toxicological assessments, single exposure by the dermal route will likely pose a low acute hazard. Single exposure to eyes may be quite irritating based on primary eye irritation studies conducted with sodium chloramben and methyl chloramben. Methyl chloramben appears to be greater ocular irritant than sodium chloramben. Swallowing a lethal dose of sodium or methyl chloramben by accident seems unlikely based on the relatively high acute oral LD_{50} values resulting from administration of the two compounds to rats. The acute inhalation toxicity hazard is also expected to be low based on the available toxicology data.

Exposure to chloramben formulations during soil application will be principally by the dermal route. Acute dermal testing with chloramben formulated products to date indicates a low acute dermal hazard.

b. Chronic Exposure

A major concern regarding any potential long-term exposure in humans to a pesticide product is the risk of developing delayed toxic effects, including cancer. In order to assess this risk for chloramben exposure, the reported conclusions of the National Cancer Institute (NCI) bioassasy of chloramben are utilized. The NCI study concluded that administration of technical chloramben resulted in hepatocellular carcinoma in female B6C3F1 mice. No other oncogenic, mutagenic, reproductive or teratogenic effects were noted in submitted studies.

The only incidence data that lends itself to risk assessment through fitting a mathematical model is that of the female mice with liver hepatocellular carcinoma.

Female Mice-Liver Hepatocellular Carcinoma Incidence

Dose (ppm)		
0	10,000	20,000
2/67 (0.03)	7/48 (0.15)	10/50 (0.20)

The dose-response relationship assumed in the analysis is that of the linear multi-stage developed by Crump whereby

$$P(D) = 1-\exp(-(q_0 + q_1 D + \ldots + q_k D^k)$$

and P is the response (incidence) and D is the dose.

The estimation of the parameter, q, by the maximum likelihood method yields the following estimator of oncogenic risk:

$$q_1 - 1.05 \times 10^{-5}$$

The model utilized (Global 79) also provides the upper and lower confidence limits for the additional risk. For a risk level of 1×10^{-6}, the upper confidence limit is estimated to be 1.59×10^{-6}. The dose producing a risk of 1×10^{-6} and the average 95% confidence limit for this dose (the virtual safe dose) are estimated to be .095 ppm and .060 ppm, respectively.

The estimation of the oncogenic risk parameter is tentative, however, given that only two data points could be utilized.

i. Dietary Exposure

By utilizing the risk parameter and determining the level of chloramben expected in the diet, the lifetime probability of a cancer due to dietary exposure can be calculated (P = qX) where X is the ppm in the diet. Table 7-1 gives the individual risks associated with ingestion of registered crops treated with chloramben.

As discussed in Chapter 6 (Residue Chemistry), the exposure of humans to chloramben residues is a function of several factors:

a. the established tolerance of the crop (in ppm).
b. percentage of crop in the daily diet.
c. percent of crop treated with chloramben.
d. average consumption of crop per person per day.
e. weight of average person (60 kg).

The estimate of human dietary exposure to chloramben as presented in Table 5-1 is 0.00045 mg/day.

Lifetime average ppm in the diet is therefore .0003 ppm.

$$\frac{.00045}{1.5} = .0003$$

TABLE 7-1

ONCOGENIC RISK ASSOCIATED WITH THE INGESTION OF CHLORAMBEN

Product	Lifetime Average ppm in Diet	Estimator of Oncogenic Risk	Lifetime Probability of Cancer Due to Ingesting Chloramben
All chloramben treated crops	3×10^{-4}	1.05×10^{-5}	3.15×10^{-9}

ii. Non-Dietary Exposure

For applicator exposure, a dietary exposure equivalent is calculated for risk assessment. Non-dietary exposure is calculated for the soluble/flowable concentrate (refer to the discussion on non-dietary exposure in Chapter 5 - Environmental Fate). The following assumptions from Chapter 5 are used in deriving the occupational risk of chloramben exposure.

1) Potential Exposure Routes and Absorption Data:

Formulation	Activity	Worst Case (mg/year)	Best Case (mg/year)
Soluble or Flowable Concentrate	Mixing-Loading (mixer-loader or farmer/planter)	27.3	0.13
	Ground Application	6.9	0.016
TOTAL:		34.2	0.146

2) A lifetime average ppm exposure (as a dietary equivalent) is calculated based on 40 years of exposure in a 70-year lifetime.

	Worst Case	Best Case
Soluble/Flowable Concentrate	0.052	0.0002

The following table gives the individual risks associated with application of chloramben formulations based on a worst-case and best-case exposure level.

TABLE 7-2

ONCOGENIC RISK ASSOCIATED WITH THE CHLORAMBEN APPLICATIONS

Product	Lifetime Average ppm Exposure	Estimator of Oncogenic Risk	Lifetime Probability of Cancer due to Chloramben Application (includes dietary)
Soluble/Flowable Concentrate			
Worst Case	0.052	1.05×10^{-5}	5.46×10^{-7} (5.49×10^{-7})
Best Case	0.0002	1.05×10^{-5}	2.10×10^{-9} (5.15×10^{-9})

3. Data Requirements and Data Gaps

The following are toxicology data requirements for registration of manufacturing-use products. Listed after each requirement is the section in the Proposed Guidelines of August 22, 1978, (43 FR, No. 163 37336) that describes the type of data required.

a. Food Use or Non-Food Use

All applicants, regardless of end-use, must submit or cite the following data:

Category of Test	Guideline Number
Acute Oral Toxicity (rat)	163.81-1
Acute Dermal Toxicity (rabbit)	163.81-2
Acute Inhalation Toxicity (rat)	163.81-3
Primary Eye Irritation (rabbit)	163-81-4
or Demonstration of pH 1-3 or 12-14	
or Demonstration of Dermal Irritation of Category I	
Primary Dermal Irritation (rabbit)	163.81-5
Skin Sensitization (guinea pig)	163.81-6

Data Gaps

Sodium Chloramben

The following tests are required for the reregistration of manufacturing-use sodium chloramben, regardless of its end-use:

Category of Test		Guideline Number
Skin Sensitization	A skin sensitization test in the guinea pig is required	163.81-6

Methyl Chloramben

The following data are required for the reregistration of manufacturing-use methyl chloramben, regardless of its end-use:

Category of Test		Guideline Number
Acute Oral	The purity of the methyl chloramben used in testing male rats must be submitted.	163.81-1
Acute Dermal Toxicity	An acute dermal toxicity study, preferably in the albino rabbit, is required.	163.81-2

Acute Inhalation Toxicity	An acute inhalation study in the rat is required.	163.81-3
Primary Eye Irritation	A primary eye irritation test in the albino rabbit is required.	163.81-4
Dermal Irritation	A dermal irritation test in the albino rabbit is required.	163.81-5
Skin Sensitization	A skin sensitization test in the guinea pig is required.	163.81-6

b. Food Use (Requires a Tolerance or Exemption)

All applicants for registration or reregistration of technical chloramben products which are formulated into end-use products intended for use on food must submit or cite the following:

Category of Test	Guideline Number
Subchronic Oral Toxicity	163.82-1
Subchronic 21-Day Dermal Toxicity	163.82-2
Dermal Sensitization	163.82-6
Chronic Feeding	163.83-1
Oncogenicity	163.83-2
Teratology	163.83-3
Reproduction	163.83-4
Mutagenicity	163.83-1 to 4
Metabolism in Laboratory Animals	163.85-1

Data Gaps

Sodium Chloramben

The following tests are required for the reregistration of manufacturing-use sodium chloramben intended for food use.

Subchronic dermal toxicity	A 21-day dermal toxicity study in the albino rabbit is required.	163.82-2
Chronic feeding	The purity of chloramben used in the 1979 chronic feeding study must be supplied.	163.83-1
Oncogenicity	Compound purity must be submitted for the 1979 rat study and 1978 mouse study.	163.83-2

Teratogenicity	Teratogenicity testing in two mammalian species is required.	163.83-3
Reproduction	Product purity is required for the exisiting reproduction study.	163.83-4
Mutagenicity	A mammalian in vitro point mutation test; a sensitive sub-mammalian point mutation test (with metabolic activation); a primary DNA damage test; and a mammalian in vitro cytogenetics test are required.	163.84-1
Metabolism	A general metabolism study in one mammalian species is required.	163.85-1

Methyl Chloramben

Provided that evidence is submitted documenting the hydrolysis of the methyl ester to chloramben acid after application to the soil, data requirements associated with the food-use pattern of methyl chloramben may be fulfilled for the most part through testing with chloramben acid or the sodium salt. The one exception is that a general metabolism study on methyl chloramben must be submitted. The data gaps detailed above for sodium chloramben pertaining to food-use must be filled in order to allow reregistration of the methyl ester in a food-use pattern.

c. Non-Food Use (Nondomestic, Outdoors)

All applicants for registration or reregistration of technical products which are formulated into end-use products intended for non-food, nondomestic, outdoor uses must submit or cite the following:

Data Gaps

Sodium Chloramben

Teratogenicity	Teratogenicity testing in two mammalian species is required.	163.83-3

Mutagenicity	A mammalian in vitro point mutation test; a sensitive sub-mammalian point mutation test; a primary DNA damage test; and a mammalian in vitro cytogenetics test are required.	163.84-1 through 163.84-4

Methyl Chloramben

Metabolism	A general metabolism is required if not submitted in conjunction with the food-use requirements	163.85-1

4. Topical Discussions

a. Sodium Chloramben

The following topical discussions describe available toxicity data on sodium chloramben and state whether they are adequate for Agency regulatory purposes.

Acute Oral Toxicity

The minimum testing needed on acute oral toxicity is one test, in the laboratory rat, on the technical chemical and on the manufacturing-use product if different.

The acute oral LD_{50} of technical chloramben (100 percent purity) was 5,620 mg/kg body weight in male rats (Hazleton Laboratories, 1959, 0022). Confidence limits could not be calculated due to an "all or none" response. Toxic effects included depression characterized by inactivity and ataxia, labored respiration, sprawling of limbs, ptosis, lack of coordination and excessive urination. Gross pathologic findings included congested lungs, kidneys and adrenals. This is an adequate determination in males, which would place technical chloramben in Category IV, indicating a very low acute oral hazard.

An acute oral LD_{50} determination using sodium chloramben (85 percent chloramben acid equivalents) administered to male and female rats suggests a similarly low acute toxicity hazard. The study is not considered to fulfill Agency requirements because of problems in determining the actual LD_{50} value.

No further testing is required given the valid LD_{50} determination for technical chloramben.

Acute Dermal Toxicity

The minimum testing needed on acute dermal toxicity is one test, preferably in the albino rabbit, on the technical chemical and manufacturing-use product.

The acute dermal LD_{50} value (intact skin) for male and female albino rabbits exposed to technical chloramben (100 percent purity) was determined to be greater than 3,160 mg/kg body weight (Hazleton Laboratories, 1959, 0023).

Depression characterized by inactivity was noted at highest dose levels. Little or no dermal absorption of the applied material was noted. Mild to moderate erythema and mild edema were observed initially, but subsided within two days. This study fulfills Agency requirements for testing on intact skin and indicates a Toxicity Category III-IV designation.

A dermal LD_{50} determination for manufacturing-use sodium chloramben (85 percent chloramben acid equivalent) applied to the intact and abraded skin of rabbits indicated a value greater than 5 g/kg body weight (CDC Research, 1978, 0065). No dermal reactions, adverse reactions or mortality were noted over the study course. A Toxicity Category IV designation is indicated. These two studies are adequate to fulfill Agency requirements for acute dermal toxicity testing. No further tests are required.

Acute Inhalation Toxicity

The minimum data requirement for acute inhalation toxicity is one test, preferably in the albino rat, on the technical chemical and on each manufacturing-use product.

No tests on technical chloramben are available.

Acute inhalation testing as conducted with sodium chloramben (82.8 percent chloramben acid equivalent) resulted in an LC_{50} determination of greater than 200 mg/l to male and female albino rats (Food and Drug Research Laboratories, 1978, 0062). This value would place sodium chloramben in Toxicity Category IV, indicating a very low acute inhalation hazard. The study is considered to fulfill Agency requirements for acute inhalation testing. No further testing is required.

Primary Eye Irritation

The minimum testing needed to evaluate eye irritation potential is one test, in albino rabbits, on each manufacturing-use product. If the test substance has a pH of 1-3 or 12-14, however, it will be judged corrosive, and an eye irritation test is not needed. Also, if the test substance has been judged to be dermally corrosive, an eye irritation test is not needed.

The acute eye irritation study on technical chloramben (100 percent purity) does not meet Agency requirements because of deficiencies in protocol. A primary eye irritation study on sodium chloramben (85 percent chloramben acid equivalent) administered to female rabbits is considered to fulfill Agency requirements for this test (CDC Research, 1978, 0064). Mild to moderate ocular irritation was observed at 24 hours in 6 of 6 rabbits. Irritation in all cases cleared within 7 days. The results indicated a slight acute eye irritation hazard based on a Toxicity Category III designation. No further testing is required.

Primary Dermal Irritation

The minimum testing needed to evaluate dermal irritation potential is one test, preferably in the albino rabbit, on each manufacturing-use product.

Sodium chloramben (85 percent chloramben acid equivalent) was very slightly irritating to intact and abraded rabbit skin at either 24 or 72 hours (CDC Research, 1978, 0063). The study is adequate to place sodium chloramben in Category IV, indicating a very low potential for dermal irritation. No further tests are required.

Skin Sensitization

The minimum requirement for assessing skin sensitization is an intradermal test in one mammalian species, preferably the guinea pig, on each manufacturing-use product.

No testing is available for either technical chloramben or manufacturing-use sodium chloramben. Tests are therefore required to assess skin sensitization.

Acute Delayed Neurotoxicity

An acute delayed neurotoxicity evaluation is not required because chloramben is not expected to cause acetylcholinesterase depression, nor is its chemical structure related to that of substances that induce delayed neurotoxicity.

Subchronic Oral Toxicity

The minimum testing needed to assess subchronic oral toxicity is one test in each of two mammalian species, a rodent and a non-rodent, on the technical chemical.

No adequate rodent subchronic (90-day) oral test of the technical product is available. A 28-day dietary feeding study in male albino rats does not fulfill Agency requirements for this test.

A two-year feeding study in male and female beagles on technical chloramben (97 percent purity) satisfies the requirement for a non-rodent study. In this study, beagle dogs received chloramben in the diet at 0, 100, 1,000 and 10,000 ppm (Hazleton Laboratories, 1963, 0028). Both test and control groups exhibited normal behavior and weight gain. Values for hematological, biochemical, and urinary analyses were within normal ranges. Organ/body weight ratios were not affected. Organs examined histologically revealed no significant alterations. Slight to slight-to-moderate vacuolation of liver cells was found in 3 of 8 dogs at the high dose level (10,000 ppm). The NOEL reported in the study is 1000 ppm (25 mg/kg body weight/day).

Because chronic testing in the mouse and rat is available, additional subchronic oral toxicity testing is not required.

Subchronic 21-Day Dermal Toxicity

The minimum requirement to assess subchronic 21-day dermal toxicity is one study, preferably in the albino rabbit, on the technical product. This study is required for all uses of chloramben.

No studies of subchronic dermal toxicity on technical chloramben are available. Testing is therefore required.

Subchronic 90-Day Dermal Toxicity

A subchronic 90-day dermal toxicity test is not required because chloramben is not purposely applied to skin, and its use will not result in human exposure comparable to, for example, the exposure of swimmers to swimming pool additives or garment wearers to pesticide-impregnated fabric.

Subchronic Inhalation

A subchronic inhalation test is not required on technical chloramben since its use would not likely result in toxic concentrations as determined from the results of the acute inhalation LC_{50} value (greater than 200 mg/l) for sodium chloramben.

Subchronic Neurotoxicity

A subchronic neurotoxicity evaluation is not required on chloramben because it is not expected to induce neuropathy or delayed neurotoxicity, and because it does not have a molecular structure closely related to that of a compound that is known to induce neuropathy or delayed neurotoxicity.

Chronic Feeding

A chronic feeding study is required in one mammalian species, preferably the laboratory rat, using the technical product.

A chronic oral toxicity study in albino rats conducted by Hazleton Laboratories (1963; 0027, 0088, 0089) will not satisfy Agency requirements because of deficiencies in study protocol and data reporting. A recently submitted chronic feeding study in Sprague-Dawley rats (Litton Bionetic, 1979, 0171) will fulfill Agency requirements following receipt of product purity information. Results of this study indicate that administration of technical chloramben at dose levels of 100, 1,000 and 10,000 ppm did not result in any dose-related chronic effects. The dose levels chosen were significantly less than the previously established MTD of approximately 32,000 ppm for rats. Body weight, food consumption, and survival were comparable among test and control animals. Results of clinical testing were negative.

Oncogenicity

Oncogenicity tests using the technical material are required in two mammalian species, normally the rat and mouse.

A National Cancer Institute (NCI) study submitted on technical chloramben (90-95 percent purity) administered for 80 weeks to Osborne-Mendel rats and B6C3F1 mice concluded that chloramben was carcinogenic to the female mice, producing hepatocellular carcinoma (National Cancer Institute, 1977, 0019). The liver in female mice was the only site where the occurrence of carcinoma was reported to be significant. The pathologic findings other than liver cell cancer do not establish a clear trend. There was some evidence that chloramben had a goitrogenic effect based on the observed incidence of follicular-cell hyperplasia of the thyroid. However, insufficient number of controls were available to draw a firm conclusion. The incidence of hemangiomas (blood vessel tumors) in male rats was significant at the low-dose level but not the high-dose level. This borderline positive supports the positive result seen in female mice. The incidence of hemangiomas in female rats was not significant at either dose level.

The study did contain some flaws in study protocol and study conduct. Among the identified deficiencies were the following: a high probability of improperly mixed feed, improperly designed exhaust vents in mixing rooms, and improperly cleaned feed-mixing pots, and feed-mixing areas. Although the study had definite shortcomings, the Agency was able to use this study in an oncogenic risk assessment. The Agency therefore considers this study adequate to fulfill requirements for oncogenic testing in both rats and mice.

The eighteen month oncogenic study of technical chloramben of unspecified purity fed to CD-1 male and female mice will supplement Agency requirements for oncogenic testing in mice following submission of the detailed composition of the test chemical (including minor impurities). In this study, chloramben was fed to CD-1 mice at levels of 0, 100, 1,000 and 10,000 ppm in the diet (Huntington Research Center, 1978, 0170). These doses were considerably below a previously determined MTD level of greater than 30,000 ppm. Behavior, appearance, and survival were considered normal and comparable between control and test animals. Differences in body weight and food consumption in treated group animals were not considered to be compound related. All organ weight values were considered to be within normal ranges and no trends were established.

Palpable masses were found primarily in male mice (all groups) and were considered to be associated with bacterial infection of the preputial gland. Primary compound associated tissue alterations were confined to the liver in all treated mice. The main hepatocellular reaction was a histomorphological alteration compatible with that observed in enzyme induction. Changes were more common in treated mice than in controls and were generally observed in a dose-dependent fashion. Secondary pathological changes associated with the compound were reflected by an increased incidence and severity of amyloidosis in high dose mice when compared to controls. Liver and kidneys from low and mid-dose mice had incidence rates much lower than the controls. Other tissue findings, including benign and malignant neoplasms, were randomly distributed among the mice at all dose levels.

The 1979 chronic feeding study discussed above (Litton Bionetics, 1979, 0171) will supplement Agency requirements for oncogenic testing in rats, provided that compound purity is submitted. The study reported no significant differences in either neoplastic or non-neoplastic lesions between control and test animals fed chloramben at concentrations of 100, 1,000, and 10,000 ppm (MTD level approximately 30,000 ppm). Neoplastic lesions were predominantly benign and occurred for the most part in the pituitary gland (chromophobe adenoma), adrenal gland (cortical adenoma), testes (interstitial cell tumor) and mammary gland (carcinoma and fibroadenoma). Spontaneous lesions of note included telangiectasis in the adrenal cortex (46 percent of these animals also exhibited cortical adenomas), degenerative cardiomyopathy, chronic inflammation of the kidneys, murine pneumonia and galactostasis and galactocele.

No further testing is required.

Teratology

The minimum requirement for evaluating a pesticide for teratogenicity is testing in two mammalian species. It is required for both food and nonfood uses of chloramben. No tests are available on chloramben to assess teratogeniceffects. Therefore, tests on two mammalian species utilizing either sodium chloramben or technical chloramben (3-amino 2,5-dichloro benzoic acid) must be submitted.

Reproduction

The minimum requirement for measuring effects on reproduction is one test using the technical chemical in the rat, lasting two generations. This is required for all food uses.

Technical chloramben (unspecified purity) fed to CFE rats at doses of 500, 1,500 and 4,500 ppm resulted in a decrease in weight gain (at the 25th week) between the F_0 and F_{2b} generations (AME Associates, 1966, 0029). Controls did not exhibit a change in weight gain over the three filial generations. In addition, at these dosages, there was also a dose-dependent trend in decreased fertility index (3 generations) and lactation index (2 generations). Provisionally, the study does not meet Agency requirements for a reproduction test. It will be judged for adequacy when the detailed composition of the test chemical is provided.

Mutagenicity

The following studies represent the minimum requirements for data on the potential heritable effects of chloramben.

1. A mammalian *in vitro* point mutation test.
2. A sensitive *sub-mammalian* point mutation test (Bacteria, fungi, insect).
3. A primary DNA damage test (i.e., sister chromatid exchange or unscheduled DNA synthesis.
4. A mammalian *in vitro* cytogenetics test. If this test suggests a positive result, a dominant lethal or heritable translocation test may be required.

After results from these test systems and other toxicology disciplines have been considered, additional testing may be required to further characterize or quantify the potential genetic risks.

A sub-mammalian point mutation test (Anderson et al., 1972, 0502) using technical chloramben (90-99 percent purity) does not fulfill Agency requirements due to the absence of a metabolic activation system and is considered supplemental.

Study results indicated that "Amiben" was not mutagenic to histidine-requiring mutants of *Salmonella typhimurium*, did not result in chemically induced mutations of the rII type in T_4 bacteriophage and did not result in reversions to the wild type in AP72 and N17 rII mutants T_4 bacteriophage.

A sub-mammalian point mutation test is still required, as well as tests designed to meet requirements 1, 3 and 4 as noted above.

Metablism in Laboratory Animals

A general metabolism study on chloramben must be carried out to fulfill Agency requirements.

A subchronic feeding study in dogs provides supplemental information on chloramben metabolism (Hazleton Laboratories, 1967, 0086). Residues were measured in tissues and excreta of dogs fed chloramben for 28 days as a working mixture of 999 parts lactose and one part Amiben (0.1 percent) prepared on a weight/weight basis. Samples of liver, kidney, muscle, fat, and blood from control and high-dose (20 ppm) animals were analyzed by gas chromatography. Residues in liver, kidney, blood, muscle, and fat were less than 0.02 ppm chloramben for both controls and high-dose animals. Chloramben residues in the urine and feces were 0.43 and 0.086 ppm, respectively, in the high-dose animals as opposed to the 0.02 ppm in the controls.

This study does not adequately investigate mammalian metabolism of chloramben and will not be considered to fulfill Agency requirements. A valid metabolism study must be submitted.

Clinical Trials

No clinical studies in humans have been conducted using chloramben. None are presently required by Agency Guidelines.

Emergency Treatment

No information is available on the prevention and treatment of chloramben intoxication.

b. Methyl Chloramben

The following topical discussions describe available toxicity data on the methyl ester of chloramben and state whether they are adequate for Agency regulatory purposes. With the exception of a metabolism study, subchronic and chronic tests required for a food-use registration of manufacturing-use methyl chloramben may be satisfied by testing on sodium chloramben or technical chloramben provided that evidence is submitted documenting the breakdown of the methyl ester to chloramben after application to the soil. Refer to Section B.4.a for topical discussions of chronic and subchronic tests performed with manufacturing-use sodium chloramben.

Acute Oral-Toxicity

The minimum testing needed on acute oral toxicity is one test, in the laboratory rat, on the technical chemical and on the manufacturing-use product if different.

The technical methyl ester of chloramben administered to male rats as a 30 percent weight/volume suspension in corn oil resulted in an LD_{50} value of 1,710 mg/kg (Hazleton Laboratories, 1966, 0024). Confidence limits were 1260-2330 mg/kg. Principal toxic effects included depression, gasping, labored respiration, ataxia, sprawling of limbs, depressed righting and placement reflexes, muscular stiffness, and death (the latter at doses of 2, 150, 4, 640 and 10,000 mg/kg). Major necropsy findings included congestion of the lungs, liver, kidneys, and pancreas; pale-appearing spleen and gastorintestinal inflammation. These results place manufacturing-use methyl chloramben in Toxicity Category III for acute oral toxicity.

This study will satisfy Agency requirements for an acute oral toxicity determination in rats following receipt of product purity.

Acute Dermal Toxicity

The minimum testing needed on acute dermal toxicity is one test, preferably in the albino rabbit, on each manufacturing-use product.

No tests on the technical methyl ester of chloramben are available. Testing on acute dermal toxicity must be submitted.

Primary Eye Irritation

The minimum testing needed to evaluate eye irritation potential is one test, in albino rabbits, on each manufacturing use product. If the test substance has a pH of 1-3 or 12-14, however, it will be judged corrosive, and an eye irritation test is not needed. If the test substance has been judged to be dermally corrosive, an eye irritation test is not needed.

No eye irritation testing has been performed with methyl chloramben. Such testing must be submitted.

Primary Dermal Irritation

The minimum testing method to evaluate dermal irritation potential is one test, preferably in the albino rabbit, on each manufacturing-use product.

No testing is available on the methyl ester of chloramben. Results of such testing must therefore be submitted.

Skin Sensitization

The minimum requirement for assessing skin sensitization is an intradermal test in one mammalian species, preferably the guinea pig, on each manufacturing-use product.

No skin sensitization test is available on methyl chloramben. Testing is therefore required.

Acute Delayed Neurotoxicity

An acute delayed neurotoxicity evaluation is not required because methyl chloramben is not expected to cause acetylcholinesterase depresssion, nor is its chemical structure related to that of substances that induce delayed neurotoxicity.

Metabolism in Laboratory Animals

A general metabolism study on methyl chloramben must be carried out to fulfill Agency requirements.

No tests are available on the metabolism of methyl chloramben. A metabolic study of manufacturing-use methyl chloramben is required in order to determine its fate in the body and potential metabolites. Data on plasma elimination must be included. Such information is necessary to assess applicator exposure risk.

Clinical Trials

No clinical studies in humans have been conducted using methyl chloramben. None are currently required under Agency Guidelines.

Emergency Treatment

No information is available on the prevention and treatment of methyl chloramben intoxication.

5. Required Labeling

Precautionary labeling of each product must correspond to the toxicity categories determined by five acute toxicity tests. Acceptable categories of acute toxicity and the corresponding required labeling are discussed in the Agency Position Chapter of this Standard.

C. Chloramben End-Use Formulations

1. Soluble Concentrate Chloramben

a. Toxicology Profile

Existing soluble concentrate chloramben end-use products (registration numbers 264-138, 264-178, 2749-202, and 264-266) contain either ammonium chloramben (23.4%) or a combination of ammonium chloramben (15.7%) and monomethylammonium chloramben (47.2%).

For purposes of chronic and subchronic toxicity testing, the Agency has determined that ammonium chloramben and monomethylammonium chloramben are equivalent to technical chloramben. Subchronic and chronic testing is not required on the ammonium or monomethylammonium salts.

The Agency has determined that technical chloramben acid and sodium chloramben are equivalent to ammonium and monomethyl ammonium chloramben for purposes of subchronic and chronic toxicity testing.

Available acute toxicity testing on ammonium and monomethyl ammonium chloramben indicate that that these salts appear to be 3 to 4 times as acutely toxic as chloramben acid. Therefore, acute oral and dermal toxicity testing on technical grade ammonium and monomethyl ammonium chloramben are required. Acute testing of end-use products is also required.

Available acutetoxicity data submitted on a soluble concentrate end-use ammonium salt formulation indicates an acute oral LD_{50} value of 7.94 ml/kg or 7,940 mg/kg (assuming a density of 1.0 g/ml) in male albino rats.

Acute toxicity testing submitted on a combination of ammonium chloramben (10.87%) and monomethylammonium chloramben (34.5%) indicates an acute oral LD_{50} value of 3.5 ml/kg or 3,500 mg/kg (assuming a density of 1.0 g/ml) in male albino rats.

A dermal LD_{50} value of 8 ml/kg or 8,000 mg/kg (assuming a density of 1.0 g/ml) in male albino rabbits was reported for this same combination of ammonium chloramben and monomethylammonium chloramben. This product resulted in slight conjunctival involvement at 24 hrs. following a 0.1 ml aliquot administration in male albino rabbits.

b. Data Requirements and Data Gaps

The Agency has determined that existing soluble concentrate end-use products containing ammonium chloramben as the sole active ingredient are substantially similar to one another for the purposes of acute toxicity testing. Data gaps identified for acute testing of such soluble concentrate products may be fulfilled through the submission of tests on an end-use soluble concentrate product containing 23.4% ammonium chloramben.

Acute toxicity tests have been submitted on a chloramben soluble concentrate formulation containing 10.8% ammonium salt and 34.5% monomethylammonium salt. The percents of active ingredient as stated do not correspond with any of the registered formulated products containing this mixture. A decision to accept this product as representative of formulations containing these salts awaits submission of further information regarding inerts in the test substance.

Data Gaps

Generic Data

Category of Test	Data Requirements	Guideline Number
Acute Oral	An acute oral toxicity test in the rat is required on technical grade ammonium and monomethyl ammonium chloramben	163.81-1
Acute Dermal	An acute dermal toxicity test in the rat is required on technical grade ammonium and monomethyl ammonium chloramben	163.81-2

Product Specific Data

Category of Test	Data Requirements	Guideline Number
Acute Oral	Test material composition and density must be submitted on the ammonium salt and ammonium (10.8%)/monomethylammonium (34.5%) salt soluble concentrates.	163.81-1
Acute Dermal	An acute dermal toxicity study, preferably in the albino rabbit, is required for an end-use soluble concentrate product containing 23.4% ammonium chloramben. Product data on the ammonium/monomethylammonium chlorambenm test substance must be submitted.	163.81-2

Acute Inhalation	An acute inhalation study in the rat is required for an end-use soluble concentrate containing 23.4% ammonium chloramben and an end-use soluble concentrate containing 15.7% ammonium chloramben and 47.2% monomethylammonium chloramben.	163.81-3
Primary Eye Irritation	A primary eye irritation test in the albino rabbit is required for a representative 23.4% ammonium chloramben product unless it has a pH of either 1-3 or 12-14 or unless it has been judged dermally corrosive. If so, it will be regulated as a corrosive substance. Product data on the ammonium/monomethylammonium chloramben test substance must be submitted.	163.81-4
Primary Dermal Irritation	A primary dermal irritation test, preferably in the albino rabbit, is required for an end-use soluble concentrate containing 23.4% ammonium chloramben. Product data on the ammonium/monomethylammonium test substance must be submitted.	163.81-5

c. Topical Discussions: Soluble Concentrate Products

Acute Oral Toxicity

The minium testing needed on acute oral toxicity is one test in the laboratory rat on each soluble concentrate end-use product.

The acute oral LD_{50} of an ammonium salt formulation of chloramben (unspecified concentration) was determined to be 7.94 ml/kg or 7940 mg/kg, assuming a density of 1.0 g/ml (Hazleton Laboratories, 1966, 0024). Confidence limits were 5.84 to 10.8 ml/kg. Principal toxic effects following administration of doses up to 21.5 ml/kg in male albino rats included depression, gasping, labored respiration, ataxia, sprawling of the limbs, depressed righting and placement reflexes, muscular stiffness and death (the latter at 10.0 and 21.5 ml/kg). Compound related necropsy findings included congestion of the lungs, kidneys, adrenal, and pancreas; pale appearing spleen; and inflammation of the diaphragm, peritoneum, and pyloric portion of the stomach. Based on these results, the product is placed in Toxicity Category IV.

This study will be considered an adequate determination of oral toxicity of an ammonium chloramben formulated product in male and female rats following identification of the specific test product, including product density.

The acute oral LD_{50} of the formulated ammonium (10.8 percent)/monomethylammonium (34.5 percent) product administered to male albino rats is 3.5 ml/kg or 3,500 mg/kg assuming a density of 1.0 g/ml (Biosearch Inc., 1969, 0001). Confidence limits were calculated at 2.4 to 5.2 ml/kg. Animal mortality occurred at least two hours following dosing and was preceded by weakness and lassitude. Data submitted separately indicate that the 3.5 ml/kg value corresponds to 1,900 mg/kg of salt and 1,680 mg/kg of acid. The high LD_{50} value places the compound in Toxicity Category III, indicating a low acute oral hazard. This study will be considered sufficient for testing the acute oral toxicity of the formulation in rats if evidence is submitted showing that the test material is representative of the registered ammonium/monomethylammonium compound. Product density must also be submitted.

Acute Dermal Toxicity

The minimum testing needed on acute dermal toxicity is one test, preferably in the albino rabbit, on each soluble concentrate end-use product.

No studies on the acute dermal toxicity of soluble concentrate end-use products containing 23.4% ammonium chloramben have been submitted.

A soluble concentrate end-use product containing 10.8% ammonium chloramben and 34.5% monomethylammonium chloramben has been tested on the intact and abraded skin of male albino rabbits at levels up to 8 ml/kg or 8,000 mg/kg, assuming on a density of 1.0 g/ml (Biosearch, Inc., 1969, 0002). There was no evidence of skin irritation at any time. Given the very high LD_{50} value a Toxicity Category IV designation is appropriate. This study will be judged for adequacy as an acute dermal determination for the registered ammonium chloramben/monomethyl ammonium chloramben soluble concentrate product following submission of composition and density of the test material.

Acute Inhalation Toxicity

An acute inhalation toxicity test is required on a soluble concentrate formulation if it causes a respirable vapor, or if 20% or more of the aerodynamic equivalent is composed of particles not larger than 10 microns. No vapor pressure data are available on chloramben products. Until data are submitted which indicate otherwise, a test will be needed on each representative chloramben soluble concentrate formulation.

Primary Eye Irritation

The minimum testing needed to evaluate eye irritation protential is one test, in albino rabbits, on each soluble concentrate product. If the test substance has a pH of 1-3 or 12-14, however, it will be judged corrosive, and an eye irritation test is not needed. If the test substance has been judged dermally corrosive, the test substance will be judged to be corrosive to the eye and an eye irritation test is not needed.

No studies on primary eye irritation have been submitted on a soluble concentrate product containing 23.4% ammonium chloramben. Such testing must be submitted.

A soluble concentrate product containing 10.8% ammonium/34.5% methylammonium chloramben was not considered to be an ocular irritant based on a 0.1 ml aliquot adminstered in male albino rabbits (Biosearch, Inc., 1969, 0003). Slight conjunctival involvement was noted at 24 hours but was negative at 48 hours. No other signs of eye irritation were noted throughout the 14-day observation period. The study is adequate to place this formulated product in Toxicity Category III, indicating a low eye irritation potential. In order to satisfy Agency requirements for testing of the ammonium/monomethylammonium chloramben soluble concentrate, product composition of the test material cited above must be submitted.

Primary Dermal Irritation

The minimum testing needed to evaluate dermal irritation potential is one test, preferably in the albino rabbit, on each soluble concentrate end-use product.

Testing on soluble concentrate formulations containing ammonium chloramben is not available and must therefore be submitted.

The previously cited study of dermal toxicity of a 10.8% ammonium/34.5% methylammonium chloramben product (Biosearch Inc., 1969, 0002) will be judged for adequacy as a dermal irritation test of the registered ammonium/monomethylammonium chloramben soluble concentrate product following submission of test material composition. No evidence of skin irritation was noted after application of the test material to either the intact or abraded skin of male albino rabbits.

Skin Sensitization

A dermal sensitization study is not required because use of the formulated product will not result in repeated human skin contact.

2. Flowable Concentrate Chloramben

a. Toxicology Profile

Two flowable concentrate end-use products, containing 83.0% sodium chloramben (registration number 264-305) and 21.0% sodium chloramben (registration number 264-306), respectively, are currently registered. The Agency has determined that acute toxicity tests submitted on manufacturing-use sodium chloramben and/or chloramben (3-amino-2,5-dichlorobenzoic acid) may be used to fulfill acute toxicity testing requirements on these flowable concentrates. Refer to the Toxicology Profile and Topical Discussions on manufacturing-use sodium chloramben for a summary of existing toxicological data on either sodium chloramben or chloramben.

b. Data Requirements and Data Gaps

None identified for flowable concentrates containing sodium chloramben.

c. Topical Discussions

Acute Oral Toxicity

The minimum testing needed on acute oral toxicity is one test in the laboratory rat on each formulated flowable concentrate product.

No tests on flowable concentrate formulations containing sodium chloramben are available. Acute toxicity testing on technical chloramben will fulfill test requirements on the flowable concentrate formulations. Refer to Section B.4.a. (Topical Discussions - Sodium Chloramben).

Acute Dermal Toxicity

The minimum testing needed on acute dermal toxicity is one test, preferably in the albino rabbit, on each formulated flowable concentrate end-use product.

No acute dermal tests are available on flowable concentrate chloramben. A dermal LD_{50} test on sodium chloramben meets Agency requirements. Refer to Section B.4.a. No further testing is required.

Acute Inhalation Toxicity

An acute inhalation toxicity test is required on a flowable concentrate formulation if it causes a respirable vapor, or if 20% or more of the aerodynamic equivalent is composed of particles not larger than 10 microns. No vapor pressure information on a chloramben product is available. Until such data are supplied, a test will be needed on flowable concentrate chloramben.

No tests of acute inhalation toxicity are available on this formulation type. However, available acute inhalation testing with sodium chloramben (refer to Section B.4.a) may be used to fulfill this test requirement for flowable concentrate end-use products.

Primary Eye Irritaiton

The minimum testing needed to evaluate eye irritation potential is one test, in albino rabbits, on each formulated flowable concentrate end-use product.

Testing on flowable concentrate formulations containing sodium chloramben is not available. A dermal irritation study using manufacturing-use sodium chloramben will fulfill Agency requirements for the flowable concentrate formulations. Refer to Section B.4.a.

Skin Sensitization

Dermal sensitization testing is not required because use of these products are not expected to result in repeated human skin contact.

D. Emulsifiable Concentrate Chloramben

a. Toxicology Profile

A single end-use product, containing 23.2% methyl chloramben (registration number 264-260), is registered in this category.

Acute toxicity tests have been conducted on a methyl chloramben emulsifiable concentrate (unspecified composition). Based on an LD_{50} determination of 5.01 ml/kg or 5,010 mg/kg (assuming a density of 1.0 g/ml) in male rats, a low acute oral hazard is expected.

Dermal testing of the formulated methyl chloramben product in rabbits at doses up to 3.16 ml/kg of body weight or 3,160 mg/kg (assuming a density of 1.0 g/ml) did not result in animal mortality. Gross signs of dermal irritation included moderate to marketed erythema at all doses on both abraded and intact skin, slight to moderate edema, and blanching.

Exposure in male and female rats to an aerosol of a formulated methyl chloramben product at a concentration of 2.0 mg/l did not cause any animal deaths. Based on a probable Toxicity Category III designation, a low acute inhalation hazard in human beings is expected.

Acute eye irritation was noted after a single application of the formulated methyl chloramben end-use products. Irritation in unrinsed eyes consisted of moderate or marked conjunctival redness, chemosis, and discharge; slight or moderate corneal opacity, slight iritis, and corneal vascularization and sloughing of epithelium. Based on these findings, the methyl chloramben end-use compound can be expected to represent an eye irritation hazard in humans.

No further tests were submitted on an emulsifiable concentrate containing methyl chloramben.

b. Data Requirements and Data Gaps

Provided that evidence is submitted indicating that the test substance described above is equivalent to the emulsifiable concentrate (23.2% methyl chloramben) currently registered, existing acute toxicity tests on the compound will be acceptable. The density of the test substance must also be submitted. The following data gaps remain.

Data Gaps

None identified for the currently registered product.

c. Topical Discussions

Acute Oral Toxicity

The minimum testing needed on acute oral toxicity is one test in the laboratory rat on the emulsifiable concentrate end-use product.

The LD_{50} value for the formulated methyl chloramben emulsifiable concentrate administered to male albino rats is 5.01 ml/kg or 5,010 mg/kg (assuming a density of 1.0 g/ml) with confidence levels from 5.84 to 10.8 ml/mg (Hazelton Laboratories, Inc., 1966, 0024). Toxic effects included depression, gasping, labored respiration, ataxia, sprawling of limbs, depressed righting and placement reflexes, muscular stiffness, bloody crust around eyes and nose, salivation and excessive urination. The necropsy findings consisted of congestion of the lungs, kidneys, adrenals, and pancreas; pale-appearing spleen; and inflammation of the diaphragm, peritoneum and pyloric portion of the stomach. This study will be considered to fulfill Agency requirements for acute oral toxicity testing in male and female rats following characterization of the compound.

No further testing is required.

Acute Dermal Toxicity

The minimum testing needed on acute dermal toxicity is one test, preferably in the albino rabbit, on the emulsifiable concentrate end-use product.

Dermal testing of the formulated methyl chloramben product in rabbits at doses up to 3.16 ml/kg of body weight did not result in animal mortality (Hazleton Laboratories, 1968, 0143). Principal toxic effects included slight depression and labored respiration in the majority of animals. One animal exhibited rapid respiration and hyperactivity. Gross signs of dermal irritation consisted of moderate to marked erythema at all doses on both abraded and intact skin, slight to moderate edema and blanching. Atonia and slight or moderate desquamation developed predominantly in the highest dose group during the course of the study and were all still present on two animals at termination. Assuming a density of 1.0 g/ml, the LD_{50} value (>3,160 mg/kg) is designated Toxicity Category III-IV. Information chacterizing the test substance (including product density) must be submitted.

Acute Inhalation Toxicity

An acute inhalation toxicity test is required on an emulsifiable concentrate product if it causes a respirable vapor, or if 20% or more of the aerodynamic equivalent is composed of particles not larger than 10 microns. No vapor pressure data are available on chloramben products. Until such data are supplied, a test will be needed on the emulsifiable concentrate containing mehtyl chloramben.

Exposure in male and female rats to an aerosol of the methyl chloramben end-use product at a concentration of 2.0 mg/l of air did not cause any animal deaths (Hazleton Laboratories, 1968, 0144). Toxic effects noted after initial exposure were restlessness, inactivity, shallow breathing and puffy and glassy eyes. Abnormalities observed upon gross necroposies included red spots, brown spots, and clear tan spots in the lungs, massive consolidation in the lungs, dark kidney medulla and discolored cervical glands. Red spots, clear tan spots, and dark brown spots were noted in the lungs of control animals. The study cannot be considered to fulfill Agency requirements for an acute inhalation toxicity determination until the product is completely characterized.

Primary Eye Irritation

The minimum testing needed to evaluate eye irritation potential is one test, in albino rabbits, on the emulsifiable concentrate end-use product. If the test substance has a pH of 1-3 or 12-14, however, it will be judged corrosive, and an eye irritation test is not needed. If the test substance has been judged to be dermally corrosive, it will also be considered corrosive to the eye and an eye irritation test is not needed.

Acute eye irritation was noted in rabbits after a single application of 0.1 ml of the formulated methyl chloramben product (Hazleton Laboratories, 1968, 0143). Principal toxic effects included blinking, preening and/or phonation immediately following dosage. Terminal weight loss was noted in one animal. Irritation in nonirrigated eyes consisted of moderate or marked conjunctival redness, chemosis and discharge; slight or moderate corneal opacity (persisting in one case beyond 7 days); slight iritis; and corneal vascularization and sloughing of epithelium (1 animal). Slight conjunctival irritation was observed in a few of the rinsed eyes. Based on these data, the compound is placed in Toxicity Category II.

A complete characterization of the test product must be provided before this study can be considered to fulfill Agency requirements.

Primary Dermal Irritation

The minimum testing needed to evaluate dermal irritation potential is one test, preferably in the albino rabbit, on the formulated emulsifiable concentrate.

Dermal irritation effects were noted during the acute dermal toxicity testing of the emulsifiable concentrate product (Hazleton Laboratories, 1968, 0143). Gross signs of dermal irritation consisted of moderate to marked erythema at all doses on both abraded and intact skin, slight to moderate edema and blanching. Atonia and slight to moderate desquamation developed predominantly in the highest dose group during the course of the study and were still present in two animals at termination. These data indicate a slight dermal irritation hazard based on a probable Toxicity Category III designation. No further testing is required.

Skin Sensitization

Dermal sensitization testing is not required because the use pattern indicates that repeated human skin contact is unlikely under conditions of use.

4. Granular Chloramben

a. Toxicity Profile

Seven granular chloramben end-use products are currently registered. Five products consist of either 1.3%, 4.3%, or 10.8% ammonium chloramben (registration numbers 264-167, 264-175, 264-191, 264-243, and 2749-169). Two products are a mix of ammonium chloramben and monomethylammonium chloramben at either a 5.4% and 17.3% level or 2.82% and 8.46% level, respectively, (registration numbers 264-251 and 264-274).

For purposes of chronic and subchronic toxicity testing, the Agency has determined that ammonium chloramben and monomethylammonium chloramben are equivalent to technical chloramben acid.

Acute oral and dermal toxicity testing is required on technical grade ammonium and monomethyl ammonium chloramben in addition to testing on end-use products.

No tests are available to assess either the acute toxicity or possible skin or eye effects of granular chloramben end-use formulations. However, the Agency has determined that granular products containing the ammonium salt of chloramben are substantially similar to soluble concentrate products containing this salt. Likewise, granular products containing a mixture of the ammonium and monomethyl ammonium salts have been determined to be substantially similar to soluble concentrate products containing these salts. Data gaps identified for soluble concentrate products are directly applicable to granular products.

b. Data Requirements and Data Gaps

The Agency has determined that existing granular end-use products containing ammonium chloramben are substantially similar to one another and to soluble concentrate chloramben products containing this salt for the purposes of acute toxicity testing. In the same respect, granular end-use products containing a mixture of ammonium chloramben and monomethylammonium chloramben are considered to be substantially similar to each other and to soluble concentrate products containing this salt. Data gaps identified for acute toxicity testing of soluble concentrate products apply also to granular chloramben products. See the Soluble Concentrate portion of this chapter for details.

c. Topical Discussions

See Topical Discussions for Soluble Concentrate products.

CHAPTER VIII

ECOLOGICAL EFFECTS OF CHLORAMBEN

A. Introduction

In order to evaluate the ecological effects of chloramben, various toxicity tests are required. Depending on the characteristics and uses of chloramben end-use formulated products, data requirements for wildlife and aquatic organisms can be completely or primarily satisfied with tests for chloramben manufacturing-use products. However, for some end-use formulations which include active ingredients different from those in the manufacturing-use products, the technical grade of each active ingredient must be used in toxicity testing. Additional tests with end-use formulations can be required if testing for manufacturing-use products is insufficient to make an adequate hazard evaluation. An evaluation of hazard to wildlife and aquatic organisms requires the assessment of risk to potentially affected non-target organisms, taking into consideration the environmental chemistry and toxicological characteristics of chloramben and its end-use formulations.

The discussion in this chapter relating to the ecological effects of chloramben is divided into two sections. In the first section the manufacturing-use products of chloramben are discussed with an ecological effects profile, a review of data requirements and gaps, and a topical review of pertinent studies. In the second section, the formulated end-use products of chloramben are grouped into generic categories which are then also discussed with ecological effects profiles, reviews of data requirements and gaps, and topical reviews. An additional feature of the second section is the application of worst-case risk assessments where adequate toxicity data permit comparisons of toxicity levels with worst-case estimates of environmental concentration levels. These risk assessments were incorporated into the appropriate ecological effects profiles.

B. Chloramben Manufacturing-Use Products

1. Ecological Effects Profile: Sodium and Methyl Chloramben

a. Sodium Chloramben

Currently available data indicate that manufacturing-use sodium chloramben is of low acute toxicity to most terrestrial wildlife. A test employing the Bobwhite Quail and the Pekin Duck found dietary LC_{50}'s to be greater than 3,160 ppm active ingredient for each species using a technical material containing 97.2 percent sodium salts of chloramben. Another test, using the Mallard Duck, found the dietary LC_{50} to exceed 4,650 ppm active ingredient with a technical material containing 91.6 percent sodium chloramben. No avian acute oral toxicity testing results are available for sodium chloramben. Tests with rats and dogs indicate a lack of acute dietary toxicity of technical chloramben to levels of 10,000 ppm (see Chapter VII). In addition, the acute oral LD_{50} for male rats was found to be 5,620 mg/kg for technical chloramben.

Currently available data also indicate that manufacturing-use sodium chloramben is of low toxicity to fish. Acute toxicity tests with Bluegill Sunfish and Rainbow Trout demonstrate 96-hour LC_{50}'s exceeding 1,000 mg/l using a technical material containing 91.6 percent sodium chloramben. Fish accumulation tests (see Chapter V) indicate that little potential exists for significant bioaccumulation of chloramben or the sodium chloramben manufacturing-use product. No studies are available on the acute toxicity of sodium chloramben to aquatic invertebrates.

b. Methyl Chloramben

Less data for toxicity to wildlife are available for the methyl chloramben manufacturing-use product than for the sodium chloramben manufacturing-use product. One test employing the Bobwhite Quail and the Pekin Duck found dietary LC_{50}'s to be greater than 3,160 ppm active ingredient for the technical methyl chloramben test material (98.8% active ingredient). No avian oral toxicity testing results or other dietary data are available. Only one oral or dietary study on mammals is available. In this study the acute oral LD_{50} to rats was found to be 1,710 mg/kg, indicating a greater toxicity for the methyl ester (see Chapter VII).

No studies have been submitted detailing aquatic toxicity tests for the methyl chloramben manufacturing-use products. However, limited data based on a letter and a memorandum, indicate that methyl chloramben may be moderately to highly toxic to aquatic organisms. Reported results include a 96-hour LC_{50} of 4 ppm for a 20 percent material with Bluegill and an indicated 24-hour LC_{50} of between 2 and 16 ppm for "amiben ester" at 2 lbs/gallon with the Fathead Minnow. The test material for these reported results is assumed to have been the methyl chloramben formulated product (Registration No. 264-260). No other data is available for fish, invertebrates, or fish accumulation.

2. Data Requirements and Data Gaps: Sodium and Methyl Chloramben

The following fish and wildlife studies testing the effects of the technical grades of sodium and methyl chloramben are required for the registration of chloramben manufacturing-use products:

Required Test	Guidelines Section
Avian Single-Dose Oral LD_{50}	163.71-1
Avian Dietary LC_{50} (2 tests)	163.71-2
Fish Acute LC_{50} (2 tests)	163.72-1
Acute Toxicity to Aquatic Invertebrates	163.72-2

a. Sodium Chloramben

Acceptable studies have been submitted for the Avian Dietary LC_{50} and Fish Acute LC_{50} tests. Data gaps exist for the following required tests:

Required Test Data Gap	Reason for Data Gap
Avian Single-Dose Oral LD_{50}	Non-submission of study.
Acute Toxicity to Aquatic Invertebrates	Non-submission of study.

Submission of studies to fill the required test data is required for completion of registration requirements for sodium chloramben manufacturing-use products.

b. Methyl Chloramben

There are no acceptable studies which have been submitted for the methyl chloramben manufacturing-use product except for the avian dietary test with an upland game species. Therefore, acceptable studies for all of the required tests for manufacturing-use products must be submitted for registration of the methyl chloramben manufacturing-use products, except that the avian dietary test need only provide data for the wild waterfowl species (preferably the Mallard Duck).

3. Topical Discussions: Sodium and Methyl Chloramben

a. Sodium Chloramben

Birds

Birds may be exposed to pesticides by feeding on pesticide granules, contaminated plants, or insects, and by dermal contact and/or inhalation when close to outdoor sprays and dust. To assess the impact of a pesticide on birds, the Agency requires certain avian toxicity tests to support the registration of pesticides. For registration of every manufacturing-use product and formulated product for outdoor application, avian acute oral LD_{50} and avian dietary LC_{50} tests are required. According to Proposed Guidelines Section 163.71-2, the avian dietary test should be conducted with an upland game bird species (preferably the Bobwhite Quail) and a wild waterfowl species (preferably the Mallard Duck). The avian single-dose Oral LD_{50} test is to be performed on one of the two species used in the avian dietary test (Proposed Guidelines Section 163.71-1).

An acceptable study meeting the requirements of the guidelines has been submitted for a test with the Mallard Duck (Wildlife Int'l, 1978, 0059). This study found a dietary LC_{50} in excess of 5,620 ppm (5,150 ppm active ingredient) for a sodium chloramben test material containing an active ingredient level of 91.6% sodium chloramben. No toxic symptoms or deaths are reported at test concentration levels up to 5,620 ppm (5, 150 ppm active ingredient). An additional acceptable study (Affiliated Medical Research, 1973, 0036) found dietary LC_{50}'s in excess of 3,160 (3,070 ppm active ingredient) for both the Bobwhite Quail and Pekin Duck. The test material in this study contained the sodium salt of chloramben (97.2 percent) as the active ingredients. No acute oral LD_{50} study has been submitted for sodium chloramben.

Freshwater Fish

The minimum data required for establishing the acute toxicity of manufacturing-use sodium chloramben for fish are determinations of 96-hour LC_{50}'s - the fish acute LC_{50} tests (Proposed Guidelines Section 163.72-1). The fish acute LC_{50} test is to be performed with a coldwater species (preferably the Rainbow Trout) and a warmwater species (preferably the Bluegill Sunfish).

Acceptable studies meeting guidelines requirements have been submitted for tests with both the coldwater and warmwater fish species. The study featuring the coldwater species (Rainbow Trout) demonstrated a 96-hour LC_{50} in excess of 1,000 mg/l (916 mg/l active ingredient) for the sodium chloramben test material containing an active ingredient level of 91.6 percent sodium chloramben (Union Carbide, 1978, 0061). No mortalities were observed at up to the 1,000 mg/l concentration level and the 96-hour no-observed-effect level (NOEL) was 100 mg/l (91.6 mg/l active ingredient). The study featuring the warmwater species (Bluegill Sunfish) demonstrated a 96-hour LC_{50} also in excess of 1,000 mg/l (916 mg/l active ingredient) for the same test material

(Union Carbide, 1978, 0060). In this test, no mortalities were observed at up to the 1,000 mg/l concentration level and the 96-hour NOEL was 180 mg/l (165 mg/l active ingredient).

Aquatic Invertebrates

A determination of the 48-hour EC_{50} for an aquatic invertebrate species is required to support the registration of all manufacturing-use products and for all formulated products intended for outdoor application (Proposed Guidelines Section 163.72-2). No study on toxicity to aquatic invertebrates has been submitted.

Other Organisms

Several other published reports on chloramben toxicity were reviewed, but conclusions about levels of toxicity cannot be verified since the test material was inadequately described. These reports include the following studies.

Published literature reported low levels of toxicity of chloramben and chloramben sodium salt to honeybees—low mortality and little effect on reproduction (Morton and Moffett, 1972, 0535; and Morton et al., 1972, 0536). Another study reported chloramben to be non-toxic to earthworms when injected with 100 mg/kg (Chio and Sanborn, 1978, 0524). A review article (Butler, 1977, 0549) indicates that toxic effects on algae occur at concentrations of 15-3000 ppm, with chloramben and its ammonium salt less toxic than the methyl ester.

b. Methyl Chloramben

Birds

As discussed in greater detail for the sodium chloramben manufacturing-use product, to assess the potential impact of a pesticide on birds, the Agency requires certain avian toxicity tests to support the registration of pesticides. The avian dietary LC_{50} test should be conducted with an upland game bird species (preferably the Bobwhite Quail) and a wild waterfowl species (preferably the Mallard Duck). The avian single-dose oral LC_{50} test is to be performed on one of the two species used in the avian dietary test.

A study (Affiliated Medical Research, 1973, 0039), acceptable in meeting guidelines requirements for testing on an upland game bird, found dietary LC_{50}'s in excess of 3,160 ppm methyl chloramben for both the Bobwhite Quail and Pekin Duck. The level of active ingredient in the test material, identified as Amiben Methyl Ester, was 98.8 percent.

Freshwater Fish

The minimum data required for establishing the acute toxicity of manufacturing-use methyl chloramben for fish are determinations of 96-hour LC_{50}'s—the fish acute LC_{50} test (Proposed Guidelines Section 163.72-1). The fish acute LC_{50} test is to be performed with a coldwater species (preferably the Rainbow Trout) and a warmwater species (preferably the Bluegill Sunfish).

Amchem Products, Inc. factory correspondence (Otten, 1970, 0146a) reports testing results on Fathead Minnows showing that after 24 hours all test fish were alive at 2 ppm and all were dead at 16 ppm. The test material is described as Amiben Ester (2 lb/gal active ingredient as methyl ester). In addition, a letter (Hughes, 1970, 0146b) reported a 96-hour LC_{50} of 4 ppm for a test material identified as Amiben Ester (as a 20 percent material). The test fish were Bluegill, and all fish were killed in 24 hours at 15 ppm. These reports are unacceptable in meeting guidelines requirements because technical materials were not used and the data are very limited.

Aquatic Invertebrates

A determination of the 48-hour EC_{50} or LC_{50} for an aquatic invertebrate species is required to support the registration of all manufacturing-use products and for all formulated products intended for outdoor application (Proposed Guidelines Section 163.72-2). No study on toxicity to aquatic invertebrates has been submitted.

Other Organisms

An unverified review article (Butler, 1977, 0549) reported that toxic effects on algae occur at concentrations of 15-3000 ppm, with the methyl ester more toxic than chloramben or ammonium chloramben.

C. Chloramben Formulated Products (for End-Use Application)

1. Soluble Concentrates

Currently registered soluble concentrate chloramben products include the following listed products.

Registration No.	Active Ingredients
264-138	23.4% Ammonium Chloramben
264-178	23.4% Ammonium Chloramben
2749-202	23.4% Ammonium Chloramben
264-266	15.7% Ammonium Chloramben and 47.2% Monomethyl-ammonium Chloramben

a. Ecological Effects Profile and Risk Assessment: Soluble Concentrates

Profile

The data previously described for the chloramben manufacturing-use products are not directly applicable to the toxicity and hazard evaluation of soluble concentrate products since these products contain ammonium chloramben and monomethyl ammonium chloramben as active ingredients. No studies have been submitted on tests using technical grades of these two active ingredients.

However, some test data on ammonium chloramben formulations (containing 23.4 percent active ingredient) serve to indicate low toxicity to wildlife and fish. In an avian dietary test with the Mallard Duck, an LC_{50} of greater than 4,650 ppm (1,090 ppm active ingredient) was found for a test material containing 23.4 percent ammonium salts of chloramben and related aminodichlorobenzoic acids. In an avian acute oral toxicity test with the Bobwhite Quail, an LD_{50} of 7.7 ml/kg was found for the same test material. Very brief fish acute toxicity testing reports indicate, in one test, a 24-hour LC_{50} greater than 50 ppm with the Fathead Minnow and another test a 96-hour LC_{50} greater than 250 ppm with Bluegill Sunfish.

In a preliminary report on testing with a test material containing 10.8 percentammonium chloramben and 34.5 percent monomethyl ammonium chloramben, 96-hour LC_{50}'s greater than 1000 ppm, 1000 ppm, and 750 ppm for Fathead Minnow, Bluegill Sunfish, and Rainbow Trout, respectively, are reported.

Risk Assessment

Only one study on the toxicity of one of the active ingredients in the soluble concentrates is of sufficient quality for use in risk analysis. A dietary LC_{50} and a no-observed-effects level (NOEL) of over 1090 ppm active ingredient in the Mallard Duck was found. Assuming a maximum broadcast application rate of 4.0 lb. active ingredient per acre (EPA's Use Pattern Summary Report for Chloramben) an environmental concentration is estimated for short rangegrass application as a hypothetical worst-case for residues on vegetation. The following table portrays the worst-case risk analysis which applies to the soluble concentrates containing only ammonium chloramben as the active ingredient:

Environmental Feature/ Species	Worst-Case Residue Conc. (ppm)	Toxicity (ppm) NOEL active	Toxicity (ppm) LC_{50} ingredient	No Effect Ratio (Residue/ NOEL)	Hazard Ratio (Residue/ LC_{50})
Short Range Grass	960				
Mallard Duck		>1090	>1090	<0.88	<0.88

Since the No-Effect Ratio and Hazard Ratio which were calculated are less than one, the ammonium chloramben soluble concentrate does not pose a likely significant risk of acute toxicity to waterfowl at current application rates.

b. Data Requirements and Data Gaps: Soluble Concentrates

The following fish and wildlife studies testing the effects of technical grade ammonium chloramben and technical grade monomethyl ammonium chloramben are required as a minimum for the registration of chloramben formulated products containing these salts:

Required Test	Guidelines Section
Avian Single-Dose Oral LD_{50}	163.71-1
Avian Dietary LC_{50} (2 tests)	163.71-2
Fish Acute LC_{50} (2 tests)	163.72-1
Acute Toxicity to Aquatic Invertebrates	163.72-2

In addition to the above-listed minimum testing requirements, additional tests can be required for registration of formulated products depending on the use pattern, mobility, persistence, toxicity, bioaccumulation, and other characteristics of the formulated product or its active ingredients. One or more of the following tests could be required; the criteria used for requirement determination are listed in the designated section of the Proposed Guidelines of July 10, 1978:

Potentially Required Test	Guidelines Section
Mammalian Acute Toxicity	163.71-3
Avian Reproduction	163.71-4
Simulated and Actual Field Testing for Mammals and Birds	163.71-5
Acute Toxicity to Estuarine and Marine Organisms	163.72-3
Embryolarvae and Life-Cycle Studies of Fish and Aquatic Invertebrates	163.72-4
Aquatic Organism Toxicity and Residue Studies	163.72-5
Simulated or Actual Field Testing for Aquatic Organisms	163.72-6

Depending on certain conditions (see Guidelines Sections 163.72-1 and 163.72-2), the Fish Acute LC_{50} and the Acute Toxicity to Aquatic Invertebrates tests could require the testing of the formulated product as well as the technical grade of the active chloramben ingredient for the registration of the respective formulated product.

For soluble concentrate products containing only ammonium chloramben, data gaps exist for every one of the six minimum required tests. For each of these tests, the technical grade of the ammonium chloramben active ingredient is to be used as the test material. Submission of these required tests is required for registration of these products.

For soluble concentrate products containing monomethyl ammonium chloramben as an active ingredient, additional data gaps exist for every one of the six minimum required tests of this additional active ingredient. For each of these additional tests, the technical grade of the monomethyl ammonium chloramben active ingredient is to be used as the test material. Submission of these required tests is necessary for registration of this product.

Due to insufficient product chemistry, environmental fate, and toxicity information, the need for any of the additional potentially required tests which have been listed cannot be determined. Following submission of studies covering the minimum registration requirements, the Agency will determine if any of the potentially required tests are necessary.

c. Topical Discussions: Soluble Concentrates

Birds

As discussed in greater detail for the sodium chloramben manufacturing-use product, to assess the potential impact of a pesticide on birds, the Agency requires at a minimum certain avian toxicity tests to support the registration of pesticides. The avian dietary LC_{50} test should be conducted with an upland game bird species (preferably the Bobwhite Quail) and a wild waterfowl species (preferably the Mallard Duck). The avian single-dose oral LD_{50} test is to be performed on one of the two species used in the avian dietary test. These tests are to be performed using the technical grade of each active ingredient.

No studies have been submitted which are acceptable in meeting these minimum requirements for registration. However, supplemental testing data (which is, however, unacceptable in meeting minimum registration requirements) is available for birds. In a good avian dietary LC_{50} test on the Mallard Duck with an ammonium chloramben formulation (Registration No. 264-138), an NOEL and an LC_{50} of greater than 4,650 ppm (1990 ppm active ingredient) were found (Truslow Farms, 1974, 0049). An avian single-dose oral LD_{50} study found an LD_{50} of 7.7 ml/kg in testing on Bobwhite Quail with the same test material (Gabriel, 1969; ID No. 0145). The latter study is of limited value because only five male birds were tested per level and little test data were reported.

Freshwater Fish

Several unpublished reports on chloramben toxicity to fish were reviewed, but conclusions about toxicity cannot be verified, because the test procedures and test material identity were unavailable.

Amchem Products, Inc. factory correspondence (Otten, 1970, 0146a) indicates a 24-hour LC_{50} exceeding 50 ppm for a soluble concentrate product (2 lb/gal active ingredient as chloramben ammonium salt) using Fathead Minnows. In addition, a letter (Hughes, 1970, 0146b) indicates a 96-hour LC_{50} in excess of 250 ppm for "Amiben" (composition unspecified) using Bluegill Sunfish. A preliminary report (Bionomics, 1970, 0051) indicates 96-hour LC_{50}s exceeding 1,000 ppm, 1,000 ppm, and 750 ppm for the Fathead Minnow, Bluegill Sunfish, and Rainbow Trout, respectively. The test material, "Amiben Concentrate," contained 10.8percent ammonium chloramben and 34.5 percent and monomethyl ammonium chloramben.

2. Flowable Concentrates

Currently registered flowable concentrate chloramben products include the following listed formulated products:

Registration No.	Active Ingredients
264-305	83.0% Sodium Chloramben
264-306	21.0% Sodium Chloramben

a. Ecological Effects Profile and Risk Assessment: Flowable Concentrates

Profile

Since the active ingredient in flowable concentrate chloramben products is sodium chloramben, the toxicity to wild organisms for both may be estimated from tests for manufacturing-use sodium chloramben (see the Ecological Effects Profile for sodium chloramben manufacturing-use product).

Risk Assessment

In the following worst-case assessment of risk to wildlife and aquatic organisms for both flowable concentrates, values for maximum hypothetical environmental concentrations of the active ingredient of the flowable concentrate products are compared with the toxicity data for various tested species. Assuming a maximum broadcast application rate of 4.0 lb/acre (EPA's Use Pattern Summary Report for Chloramben), environmental concentrations are estimated for direct application to water, for field runoff water, and for short range grass (as hypothetical worst-case situations for residues of the flowable concentrate products). The No Observed Effects Levels (NOEL's) and LC_{50}'s for various fish and wildlife are taken from valid studies described previously for the sodium chloramben manufacturing-use product. The following table portrays the worst-case risk analysis which applies to both the flowable concentrate products:

Environmental Feature/ Species	Worst-Case Residue Conc. (ppm)	Toxicity (ppm)		No Effect Ratio (Residue/ NOEL)	Hazard Ratio (Residue/ LC_{50})
		NOEL(ai)	LC_{50}(ai)		
Water Receiving Direct Application*					
Bluegill Sunfish	2.94	165	>916	0.018	<0.0032
Rainbow Trout	2.94	91.6	>916	0.032	<0.0032
Runoff Water**					
Bluegill Sunfish	1.77	165	>916	0.011	<0.0019
Rainbow Trout	1.77	91.6	>916	0.019	<0.0019
Short Range Grass					
Mallard Duck	960	>5150	>5150	<0.19	<0.19
Bobwhite Quail	960	N.A.	>3070	N.A.	<0.31

N.A. = Not available.
* = Assumes complete mixing in a six inch layer of standing water.
** = Assumes 10% of application in one inch of runoff water.

Since the No-Effect Ratios and Hazard Ratios which were calculated are substantially less than one, sodium chloramben flowable concentrates do not pose a likely significant risk of acute toxicity to fish or birds at current application rates of 4 pounds active ingredient per acre. Based on toxicological testing with mammals (see Chapter VII), the hazard to mammals is also judged to be insignificant. There are no data available to evaluate the hazard to aquatic invertebrates. Data described in Chapter V for chloramben (acid form) indicate little potential for significant bioaccumulation in fish.

b. Data Requirements and Data Gaps: Flowable Concentrates

The minimum required tests and potentially required tests for registration of flowable concentrates are the same as for all formulated pesticide products and have been discussed already for the soluble concentrates. Since flowable concentrate products contain only sodium chloramben as active ingredient, tests submitted and described for the sodium chloramben manufacturing-use product also serve to fulfill the minimum testing requirements for flowable concentrates.

Therefore, the data gaps in the minimum testing requirements for flowable concentrates containing sodium chloramben are the same as for the sodium chloramben manufacturing-use product:

Required Test Data Gap	Reason for Data Gap
Avian Single-Dose Oral LD_{50}	Non-submission of study.
Acute Toxicity to Aquatic Invertebrates	Non-submission of study.

Submission of tests to fill in these data gaps is required for registration of the flowable concentrate products. Due to insufficient product chemistry, environmental fate, and toxicity information, the need for any of the additional potentially required tests cannot be determined. Following submission of studies covering the minimum registration requirements, the Agency will determine if any of the potentially required tests are necessary.

c. Topical Discussions: Flowable Concentrates

See the Topical Discussions section for the sodium chloramben manufacturing-use product for topical discussions relevant to the flowable concentrate products. No studies have been submitted for the flowable concentrate products per se.

3. Emulsifiable Concentrate

The currently registered emulsifiable concentrate chloramben product is the following formulated product:

Registration No.	Active Ingredients
264-260	23.2% Methyl Chloramben

a. Ecological Effects Profile and Risk Assessment: Emulsifiable Concentrates

Profile

Since the active ingredient in the chloramben emulsifiable concentrate product is methyl chloramben, the toxicity to wild organisms may be estimated from tests for the manufacturing-use methyl chloramben (see the Ecological Effects Profile for methyl chloramben manufacturing-use product).

Risk Assessment

With the exception of the dietary data on an avian upland game species, Bobwhite Quail, no data were available on the toxicity of methyl chloramben for a risk assessment. In the following worst-case assessment of risk to wildlife, for the emulsifiable concentrate, the value for maximum hypothetical environmental concentrations of the active ingredient of the emulsifiable concentrate product is compared with the toxicity for the avian upland game species.

Assuming a maximum broadcast application rate of 3.0 pounds active ingredient per acre (EPA's Use Pattern Summary Report for Chloramben), environmental concentrations are estimated for short range grass (as the hypothetical worst-case situation for residues of the emulsifiable concentrate product). The NOEL and LC_{50} for Bobwhite Quail are taken from the valid study described previously for the methyl chloramben manufacturing-use product. The following table portrays the worst-case risk analysis which applies to the emulsifiable concentrate product:

Environmental Worst-Case

Feature/ Species	Residue Conc. ppm	Toxicity NOEL active	LC$_{50}$ ingredient	No Effect Ratio (Residue/ NOEL)	Hazard Ratio (Residue/ LC$_{50}$)
Short Range Grass	720				
Bobwhite Quail		>3120	>3120	<0.23	<0.23

Since the No-Effect Ratio and Hazard Ratio which were calculated are substantially less than one, methyl chloramben emulsifiable concentrate does not pose a likely significant risk of acute toxicity to birds at current application rates of 3 pounds active ingredient per acre. Based on toxicological testing with mammals (see Chapter VII), the hazard to mammals is also judged to be insignificant. There are no data available to evaluate the hazard to fish or aquatic invertebrates.

b. Data Requirements and Data Gaps: Emulsifiable Concentrate

The minimum tests and potentially required tests for registration of emulsifiable concentrates are the same as for all formulated pesticide products and have been discussed already for the soluble concentrates. Since the emulsifiable concentrate products contain only methyl chloramben as the active ingredient, tests submitted for registration of the methyl chloramben manufacturing-use product would also serve to fulfill the minimum testing requirements for the emulsifiable concentrates.

With the exception of an acceptable avian dietary LC$_{50}$ with an upland game bird species, no acceptable studies have been submitted for the methyl chloramben manufacturing-use product. Therefore the data gaps in the minimum testing requirements for the emulsifiable concentrates are the same as for the methyl chloramben manufacturing-use product. Submission of tests to fill in these data gaps is required for registration of the emulsifiable concentrate products.

Due to insufficient product chemistry, environmental fate, and toxicity information, the need for any of the additional potentially required tests cannot be determined. Following the submission of studies covering the minimum registration requirements, the Agency will determine if any of the potentially required tests are necessary.

c. Topical Discussions: Emulsifiable Concentrate

See the Topical Discussions section for the methyl chloramben manufacturing-use product for topical discussions relevant to emulsifiable concentrate products.

4. Granular Chloramben

Currently registered granular chloramben products include the following listed formulated products:

Registration No.	Active Ingredients
264-167	10.8% Ammonium Chloramben
264-175	10.8% Ammonium Chloramben
264-191	1.3% Ammonium Chloramben
264-243	4.3% Ammonium Chloramben
2749-169	10.8% Ammonium Chloramben
264-251	5.4% Ammonium Chloramben and 17.3% Monomethyl ammonium Chloramben
264-274	2.82% Ammonium Chloramben and 8.46% Monomethyl ammonium Chloramben

a. Ecological Effects Profile and Risk Assessment Granular

Profile

Since granular chloramben products contain ammonium chloramben or ammonium chloramben with monomethyl ammonium chloramben as active ingredients (as do the soluble concentrate formulated products), the ecological effects profile of the soluble concentrates is directly applicable to granular products and will not be repeated here. Granular products, however, can pose a unique hazard to birds. Birds may selectively pick up granules as food or as grit for incorporation into their gizzards. An evaluation of this hazard cannot be made, however, without the required toxicity data for birds.

Risk Assessment

There are insufficient toxicity data for any sort of risk assessment for wildlife or aquatic organisms.

b. Data Requirements and Data Gaps: Granular

The minimum data requirements for granular products are the same as those for the soluble concentrates. Fulfillment of data gaps which have been identified for the soluble concentrates will serve to fulfill the minimum data requirements for the granular products at the same time. Testing is required on technical grade ammonium and technical grade monomethyl ammonium chloramben.

However, due to insufficient product chemistry, environmental fate, and toxicity information, the need for any of the additional potentially required tests cannot be determined. Following the submission of studies covering minimum registration requirements, the Agency will determine if any of the potentially required tests are necessary.

c. Topical Discussions: Granular

Refer to the Topical Discussion section for the soluble concentrates for topical discussions relevant to the granular products.

GUIDE TO USE OF BIBLIOGRAPHY

Guide to Use of This Bibliography

1. Content of Bibliography. This bibliography contains citations of all the studies reviewed by EPA in arriving at the positions and conclusions stated elsewhere in this standard. The bibliography is divided into 3 sections: (1) citations that contributed information useful to the review of the chemical and considered to be part of the data base supporting registrations under the standard, (2) citations examined and judged to be inappropriate for use in developing the standard, and (3) standard reference material. Primary sources for studies in this bibliography have been the body of data submitted to EPA and its predecessor agencies in support of past regulatory decisions, and the published technical literature.

2. Units of Entry. The unit of entry in this bibliography is called a "study". In the case of published materials, this corresponds closely to an article. In the case of unpublished materials submitted to the agency, the Agency has sought to identify documents at a level parallel to a published article from within the typically larger volumes in which they were submitted. The resulting "studies" generally have a distinct title (or at least a single subject), can stand alone for purposes of review, and can be described with a conventional bibliographic citation. The Agency has attempted also to unite basic documents and commentaries upon them, treating them as a single study.

3. Identification of Entries . The entries in this bibliography are sorted by author, date of the document and title. Each entry bears, to the left of the citation proper, a four digit identifier preceeded by a colon (ie. :0039). At the top of each section of this bibliography is an alpha-numeric identifier (GS 0086:). These identifiers are joined to complete the identification number for a citation (ie. GS-0086:0039). These numbers are called "Temporary Record Identifiers", or TRID's,and they should be used at any time a specific reference is required.

4. Form of the Entry. In addition to the Temporary Record Identifier (TRID), each entry consists of a bibliographic citation containing standard elements followed, in the case of materials submitted to EPA, by a description of the earliest known submission. The bibliographic conventions used reflect the standards for the American National Standards Institute (ANSI), expanded to provide for certain special needs. Some explanatory notes of specific elements follow:

   a. Author. Whenever the Agency could confidently identify one, the Agency has chosen to show a personal author. When no individual was identified, the Agency has shown an identificable laboratory or testing facility as author. As a last resort, the Agency has shown the first known submitter as author.

   b. Document Date. When the date appears as four digits with no question marks, the Agency took it directly from the document. When a four-digit date is followed by a question mark, the bibliographer deduced the date from evidence in the document. When the date appears as (19??), the Agency was unable to determine or estimate the date of the document.

c. Title. This is the third element in the citation. In some cases it has been necessary for the Agency bibliographers to create or enhance a document title. Any such editorial insertions are contained between square brackets.

d. Trailing Parenthesis. For studies submitted to us in the past, the trailing parenthesis include (in addition to any self-explanatory text) the following elements describing the earliest known submission.

(1) Submission Date. Immediately following the word 'received' appears the date of the earliest known submission.

(2) Administrative Number. The next element, immediately following the word 'under', is the registration number, experimental permit number, petition number, or other administrative number associated with the earliest known submission.

(3) Submitter. The third element is the submitter, following the phrase 'submitted by'. When authorship is defaulted to the submitter, this element is omitted.

(4) Volume Identification. The final element in the trailing parenthesis identifies the EPA accession number of the volume in which the original submission of the study appears. The six-digit accession number follows the symbol 'CDL', standing for "Company Data Library". This accession number is in turn followed by an alphabetic suffix which shows the relative position of the study within the volume. For example, within accession number 123456, the first study would be 123456-A; the second, 123456-B; the 26th, 123456-Z; and the 27th 123456-AA.

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